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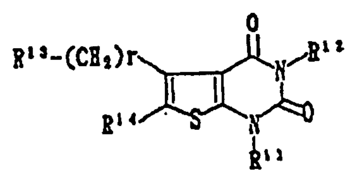
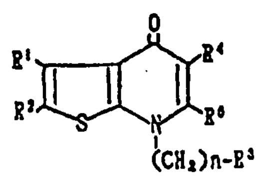


(I)



(II)

(57) Abstract

A gonadotropin-releasing hormone antagonistic composition, which comprises an optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5 to 7 membered ring and a homo or hetero 5 to 7 membered ring such as compounds of formulae (I) or (II) is effective as a propylactic or therapeutic agent for the prevention or treatment of several hormone dependent diseases, for example, a sex hormone dependent cancer (e.g. prostatic cancer, cancer of the uterine cervix, breast cancer, pituitary adenoma), benign prostatic hypertrophy, myoma of the uterus, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, polycystic ovary syndrome and acne vulgaris; is effective as a fertility controlling agent in both sexes (e.g. a pregnancy controlling agent and a menstrual cycle controlling agent); can be used as a contraceptive of male or female, as an ovulation-inducing agent of female; can be used as an infertility treating agent by using a rebound effect owing to a stoppage of administration thereof; is useful as modulating estrous cycles in animals in the field of animal husbandry, as an agent for improving the quality of edible meat or promoting the growth of animals; is useful as an agent of spawning promotion in fish.

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DESCRIPTION

BICYCLIC THIOPHENE DERIVATIVES AND USE AS GONADOTROPIN RELEASING HORMONE ANTAGONISTS

Technical Field

The present invention relates to a pharmaceutical composition for antagonizing a gonadotropin-releasing hormone (GnRH) containing a condensed-bycyclic compound consisting of a homo or hetero 5 to 7-membered ring group and a homo or hetero 5 to 7-membered ring group. The present invention also relates to novel condensed-ring thiophene derivatives and salts thereof. The present invention further relates to methods for manufacturing the novel condensed-ring thiophene derivatives and the salts thereof.

Background Art

Secretion of anterior pituitary hormone undergoes the control by peripheral hormone secreted from target organs for the respective hormones and by secretion-accelerating or -inhibiting hormone from hypothalamus, which is the upper central organ of anterior lobe of pituitary (in this specification, these hormones are collectively called "hypothalamic hormone"). At the present stage, as hypothalamic hormones, nine kinds of hormones including, for example, thyrotropin releasing hormone (TRH) or gonadotropin releasing hormone {GnRH: sometimes called as LH-RH (luteinizing hormone releasing hormone)} are confirmed their existence (cf. Seirigaku 2, compiled by M. Iriku and K Toyama, published by Bunkohdo, p610-618, 1986). These hypothalamic hormones are assumed to show their actions via the receptor which is considered to exist in the anterior lobe of pituitary (cf. ibid), and observatinal studies of receptor genes specific to these hormones,

including cases of human, have been developed (Receptor Kiso To Rinshô, compiled by H. Imura, et al., published by Asakura Shoten, p297-304, 1993). Accordingly, antagonists or agonists specifically and selectively acting on these receptors control the action of hypothalamic hormone and controlling the secretion of anterior pituitary hormone. As the results,they are expected to be useful for prophylactic and therapeutic agents of anterior pituitary hormone dependent diseases.

Leuprorelin acetate [Fujino et al., Biological and Biophysical Research Communications, Vol.60, 00.406-413, 1974); Oliver, R.T.D. et al., British Journal of Cancers, Vol.59, p.823, 1989; and Toguchi et al., Journal of International Medical Research, Vol.18, pp.35-41], which is a highly potent derivative of gonadotropic hormone-releasing hormone, one of the hypothalamic hormones, (hereinafter sometimes abbreviated as GnRH) [Schally A. V. et at., Journal of Biological Chemistry, Vol. 246, pp.7230-7236, 1971; and Burgus, R. et al., Proceeding of Natural Academic Science, USA, Vol.69, pp278-282, 1972], by administration of multiple doses, lowers release.production of gonadotropic hormone in pituitary, causing lowering of reactivity on gonadotropic hormone is spermary and ovary to suppress secretion of testosterone and estrogen. Leuprorelin acetate has, therefore, been known to show antitumor activity on such hormone-dependent cancers as exemplified by prostate cancer, and has been widely used in the clinical field. Leuprorelin acetate has been widely used clinically also as a therapeutic agent of e.g. endometriosis and precocious puberty. The high antitumor activity of leuprorelin acetate is assumed to be due to its high resistance, as compared with natural GnRH, against protease,and to high affinity to

GnRH receptor causing desensitization of GnRH due to decrease in number of receptors. However, as leuprorelin acetate is an ultra-agonist on GnRH receptor, it has been known that, immediately after the first administration, a transient aggravation accompanied with the rise of serum testosterone concentration due to pituitary-gonadotropic action (acute action) is observed. Circumstances being such as above, GnRH antagonistic drugs which are expected to have substantially the same therapeutic effects as described above but not to cause the above-mentioned transient pituitary-gonadotropic action (acute action) have been desired. As compounds having such GnRH antagonistic activity, a number of compounds including, for example, derivatives of GnRH such as straight-chain peptides, (USP 5140009, 5171835), cyclic hexapeptide derivatives [JPA S61(1986)-191698] or bicyclic peptide derivatives [Journal of medicinal chemistry, Vol.36, pp.3265-3273, 1993]. These compounds are, however, all peptides, which leave many problems including, for example, dosage forms, stability of drugs, durability of actions and stability on metabolism. For solving these problems, orally administrable GnRH antagonistic drugs, especially non-peptide ones, are strongly desired. At the present stage, however, no report on non-peptide GnRH antagonistic drugs has been made.

The object of the invention lies in providing novel compounds having excellent gonadotropic hormone releasing hormone antagonistic activity as well as excellent gonadotropic hormone releasing hormone antagonistic agents.

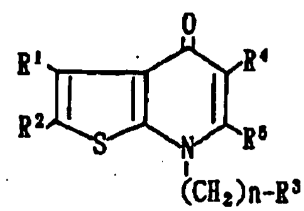
Disclosure of Invention

Thus, the present invention provides a pharmaceutical composition for antagonizing a gonadotropin-releasing hormone (GnRH) containing a

condensed-bicyclic compound consisting of a homo or hetero 5 to 7 membered ring and a homo or hetero 5 to 7 membered ring. The present invention also provides novel condensed-ring thiophene derivatives and salts thereof. The present invention further provides methods for manufacturing the novel condensed-ring thiophene derivatives and the salts thereof.

More specifically, the present inveniton provides:

(1) A compound of the formula (I):



(I)

wherein R^1 and R^2 are each independently hydrogen or a group bonded through a carbon atom, a nitrogen atom or a sulfur atom;

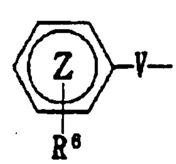
R^3 is an optionally substituted homo- or hetero-cyclic group;

R^4 is hydrogen, formyl, cyano a lower alkyl group substituted by a group bonded through a sulfur atom or an optionally substituted hydroxyl group, a carbonyl group which may be substituted with an optionally substituted hydrocarbon residue, an esterified or amidated carboxyl group;

R^5 is hydrogen or a group bonded through a carbon atom;

n is 0 to 3;

with the proviso that the homo- or hetero-cyclic group shown by R^3 is not substituted by a group, which is described in EP-A-443568 and EP-A-520423, of the formula:



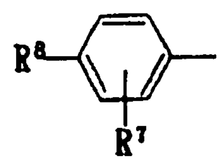
in which R^6 is an optionally substituted 5 to 7 membered heterocyclic group having as a group capable of constituting the ring, carbonyl, thiocarbonyl, an optionally oxidized sulfur atom or a group convertible them, a group capable of forming an anion or a group convertible into an anion;

Z is an optionally substituted aromatic hydrocarbon residue optionally containing a hetero atom or an optionally substituted heterocyclic group;

V is a chemical bond or a spacer group,

or a salt thereof,

(2) a compound according to (1), wherein R^3 is a group of the formula:



in which R^7 is hydrogen, halogen or a group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulfur atom;

R^8 is hydrogen, halogen, nitro, cyano or a hydrocarbon residue which may be substituted by a group bonded through an oxygen atom, a nitrogen atom or a sulfur atom,

(3) a compound according to (1), wherein either one of R^1 or R^2 is a group of the formula:

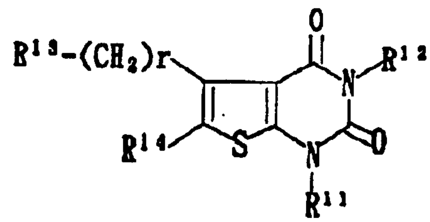
$$R^9-(CH_2)m-$$

in which R^9 is a group bonded through a nitrogen atom; m is 0 to 3, and the other one is a group of the formula:

$$R^{10}-A-$$

in which R^{10} is an optionally substituted phenyl; A is a chemical bond or a spacer group,

(4) a compound of the formula (II):



(II)

wherein R^{11} is hydrogen, lower alkyl, a group of the formula:

$$Q-(CH_2)p-$$

in which Q is aryl which may be substituted by a) halogen, b) nitro, c) cyano, d) amino, e) an optionally substituted f) carboxyl, lower alkylenedioxy or g) a group of the formula: $-A-R^{15}$ in which A is a chemical bond or a spacer group, R^{15} is alkyl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group;

R^{12} is hydrogen, alkyl, an optionally substituted aryl, an optionally substituted aralkyl, an optionally substituted cycloalkyl; R^{13} is an optionally substituted amino,;

R^{14} is an optionally substituted aryl;

r is 0 to 3,

or a salt thereof,

(5) a compound according to (4), wherein R^{11} is a group of the formula:

$$Q-(CH_2)-p-$$

in which Q is aryl which may be substituted by a) halogen, b) nitro, c) cyano, d) amino, e) an optionally substituted f) carboxyl, lower alkylenedioxy or g) a group of the formula $-A-R^{15}$ in which A is a chemical bond or a spacer group, R^{15} is alkyl,

(6) a compound according to (4), wherein Q is aryl which may be substituted by halogen,

(7) a compound according to (4), wherein R^{13} is optionally substituted mono-aralkylamino,

(8) a compound according to (4), wherein R^{13} is optionally substituted benzylamino,

(9) a compound according to (4), wherein R^{14} is optionally substituted phenyl,

(10) a compound which is 3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2-methoxybenzyl)-2-(4-methoxyphenyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester of its salt,

(11) a compound which is 3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2-fluorobenzyl)-2-(4-methoxyphenyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester or its salt,

(12) a compound which is 2-(4-acetylaminophenyl)-3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2-fluorobenzyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester or its salt,

(13) a compound which is 5-benzylaminomethyl-1-(2-chloro-6-fluorobenzyl)-2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-3-phenylthiion[2,3-d]pyrimidine or its salt,

(14) a compound which is 5-benzoyl-3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro--4-oxo-2-(4-propionylaminophenyl)thieno[2,3-b]pyridine or its salt,

(15) a compound which is 5-benzoyl-3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine or its salt,

(16) a compound which is 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-5-isobutyryl-4-oxo-2-(4-propionylaminophenyl)-thieno[2,3-b]pyridine or its salt,

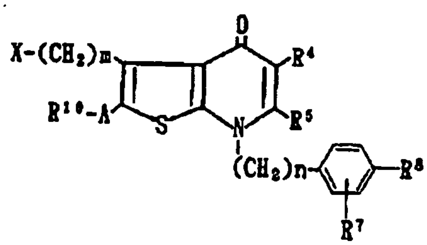
(17) a compound which is 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-5-isobutyryl-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine or its salt,

(18) a compound which is 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine-5-(N-isopropyl)carboxamide or its salt,

(19) a compound which is 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine-5-(N-isopropyl-N-methyl)carboxamide or its salt,

(20) a compound which is 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine-5-(N-benzyl-N-methyl)carboxamide or its salt,

(21) a method for producing a compound of (3), which comprises reacting a compound of the formula (III):



(III)

wherein R^4, R^5 and n are the same meaning as defined in (1);

R^7 and R^8 are the same meaning as defined in (2);

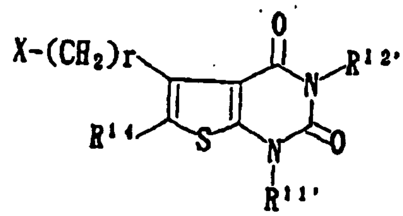
R^{10} and m are the same meaning as defined in (3);

X is a leaving group; or a salt thereof, with a compound of the formula:

$$R^9H$$

wherein R^9 is the same meaning as defined in (3), or a salt thereof,

(22) a method for producing a compound of (5), which comprises reacting a compound of the formula (IV):



(IV) .

wherein $R^{11'}$ is a group of the formula:

$Q-(CH_2)p-$

in which Q is aryl which may be substituted by a) halogen, b) nitro, c) cyamo, d) amino, e) an optionally substituted f) carboxyl, lower alkylenedioxy or g) a group of the formula: -A- R^{15} in which A is a chemical bond or a spacer group, R^{15} is alkyl;

$R^{12'}$ is alkyl, optionally substituted aryl, optionally substituted ararkyl or optionally substituted cycloalkyl;

R^{14} and r are the same meaning as defined in claim 4;

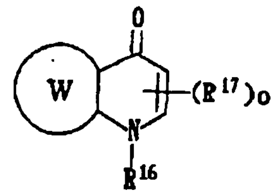
X is a leaving group; or a salt thereof, with a compound of the formula:

$R^{13}H$

wherein R^{13} is the same meaning as defined in (4), or a salt thereof,

(23) a gonadotropin-releasing hormone antagonistic composition, which comprises an optionally substituted condensed-bycyclic compound consisting of a homo or hetero 5 to 7 membered and a homo or hetero 5 to 7 membered ring; carrier; excipient or diluent,

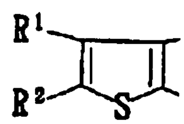
(24) a composition according to (23), wherein the optionally substituted condensed-bicyclic compound is a compound of the formula (IV):



(V)

in which a ring W is an optionally substituted homo or hetero 5 to 7 membered ring; R^{16} is an optionally substituted hydrocarbone residue; R^{17} is hydrogen, or a group bonded through a carbon atom, a nitrogen atom, oxygen atom or sulfur atom; o is 1 or 2,

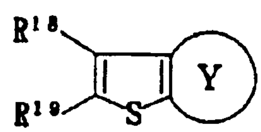
(25) a composition according to (24), wherein the ring W is a ring the formula (VI):



(VI)

in which R^1 and R^2 are each independently hydrogen, or a group bonded through a carbon atom, a nitrogen atom, oxygen atom or a sulfur atom,

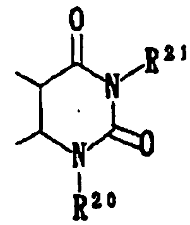
(26) a composition according to (23), wherein the optionally substituted condensed-bicyclic compound is a compound of the formula (VII):



(VII)

in which a ring Y is an optionally substituted hetero 5 to 7 membered ring; R^{18} and R^{19} are each independently an optionally substituted hydrocarbon residue,

(27) a composition according to (26), wherein the ring Y is a ring of the formula (VIII):



(VIII)

in which R^{20} and R^{21} are each independently hydrogen, an optionally substituted hydrocarbon residue,

(28) a composition according to (23), which is a composition for preventing or treating a sex hormone dependent disease,

(29) a composition according to (23), which is a composition for preventing or treating a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus,

(30) a composition according to (29), wherein the sex hormone dependent cancer is selected from the group consisting of prostatic cancer, uterus cancer, breast cancer and pitutiary adenoma,

(31) a composition according to (28), wherein the sex hormone depending disease is selected from the group consistion of prostatauxe, endometriosis, myoma uteri and prococious puberty,

(32) a pregnancy controlling composition, which comprises a compound or a salt thereof claimed in (23), carrier, excipient or diluent,

(33) a menstrual cycle controlling composition, which comprises a compound or a salt thereof claimed in (23), carrier, excipient or diluent, and

(34) a composition according to (32), which is a composition for contraception,

(35) a method for antagonizing gonadotropin-releasing hormone in a mammal in need thereof comprising administering an effective amount of a composition according to (23) to a mammal suffering from a

gonadotropin-releasing hormone derived disorder, (36) a method according to (35), wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent disease, (37) a method according to (35), wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent cancer, benign prostatic hypertropy or myoma of the uterus, (38) a method according to (37), wherein the sex hormone dependent cancer is selected from the group consisting of prostatic cancer, uterus cancer, breast cancer and pitutiary adenoma, (39) a method according to (36), wherein the sex hormone depending disease is selected from the group consisting of prostatauxe, endometriosis, myoma uteri and precocious puberty, (40) a method for controlling pregnancy in a mammal in need thereof comprising administering an effective amount of a composition according to (23), (41) a method for controlling menstrual cycle in a mammal in need thereof comprising administering an effective amount of a composition according to (23), (42) a method for contraception in a mammal in need thereof comprising administering an effective amount of a composition according to (23), (43) a use of an optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5 to 7 membered ring and a homo or hetero 5 to 7 membered ring for producing a gonadotropin-releasing hormone antagonistic composition for antagonizing gonadotropin releasing hormone in a mammal suffering from a gonadotropin-releasing hormone derived disorder, (44) a use according to (43), wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent disease, (45) a use according to (43), wherein the gonadotropin-

releasing hormone derived disorder is a sex hormone dependent cancer, benign prostatic hypertropy or myoma of the uterus,

(46) a use according to (45), wherein the sex hormone dependent cancer is selected from the group consisting of prostatic cancer, uterus cancer, breast cancer and pututiary adenoma,

(47) a use according to (45), wherein the sex hormone depending disease is selected from the group consisting of prostatauxe, endometriosis, myoma uteri and precocious puberty,

(48) a use of an optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5 to 7 membered ring and a homo or hetero 5 to 7 membered ring for producing a gonadotropin-releasing hormone antagonistic composition for controlling pregnancy in a mammal in need thereof,

(49) a use of an optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5 to 7 membered ring and a homo or hetero 5 to 7 membered ring for producing a gonadotropin-releasing hormone antagonistic composition for controlling menstrual cycle in a mammal in need thereof, and

(50) a use of an optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5 to 7 membered ring and a homo or hetero 5 to 7 membered ring for producing a gonadotropin-releasing hormone antagonistic composition for contraception in a mammal in need thereof.

Examples of the groups bonded through the carbon atom shown by R^1, R^2, R^5 and R^7, include, each optionally substituted, alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl), cycloalkyl (e.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclopentyl and cyclohexyl), alkoxyalkyl (e.g. C_{1-3} alkoxy-C_{1-6} alkyl such as

methoxymethyl, ethoxymethyl, ethoxybutyl and propoxyhexyl), hydroxyalkyl (e.g. C_{1-6} alkyl such as hydroxymethyl, hydroxyethyl, hydroxybutyl and hydroxypropyl), alkenyl (e.g. C_{2-6} alkenyl such as vinyl,butadienyl and hexatrienyl), formyl, carboxyl, alkoxycarbonyl (e.g. C_{1-6} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and t-butoxycarbonyl), cyano, amido, mono-, di-alkylcarbamoyl (e.g. mono-, di-C_{1-6} alkylcarbamoyl such as methyl carbamoyl, ethylcarbamoyl, hexylcarbamoyl, dimethylcarbamoyl and methylethylcarbamoyl), amidino, aryl (e.g. C_{6-14} aryl such as phenyl,naphthyl and anthracenyl), aralkyl (e.g. C_{7-20} aralkyl such as benzyl, benzhydryl and trityl) and heterocyclic groups having a bond at the carbon atom (e.g. 5-membered cyclic groups containing, besides the carbon atom, 1 to 4 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl and 1H- or 2H-tetrazolyl; 6-membered cyclic groups containing, besides the carbon atom, 1 to 4 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as N-oxido-2-, 3- or 4-pyridyl, 2-, 4-or 5-pyrimidinyl, N-oxido-2-, 4- or 5-pyrimidinyl, 2- or 3-thiomorpholinyl, 2- or 3-morpholinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, piperidinyl, pyranyl, thiopyranyl, 1,4-oxadinyl, 1,4-thiazinyl, 1,3-thiazinyl, 2- or 3-piperazinyl, triazinyl, oxotriazinyl, 3- or 4-pyridazinyl, pyrazinyl and N-oxido-3- or 4-pyridazinyl; and 5- to 8-membered cyclic groups or condensed ring

thereof containing, besides the carbon atom, 1 to 4 hetero-atoms e.g. oxygen atom, sulfur atom or nitrogen atom, for example, bicyclic or tricyclic condensed cyclic groups containing, besides the carbon atom, 1 to 4 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as benzofuryl, benzothiazolyl, benzoxazolyl, tetrazolo[1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, benzoimidazolyl, quinolyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthylizinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acrydinyl, phenanthridinyl, chromanyl, benzoxazinyl, phenazinyl, phenothiazinyl and phenoxazinyl).

Examples of the substituents, which the above-mentioned groups bonded through the carbon atom may have, include C_{6-14} aryl (e.g. phenyl and naphthyl) optionally substituted with 1 to 4 substituents selected from, for example, (a) hydroxyl, (b) amino, (c) mono- or di- C_{1-6} alkyl amino (e.g. methylamino, ethylamino, propylamino, propylamino, dimethylamino and diethylamino) and (d) C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy and hexyloxy) and (e) halogen (fluorine, chlorine, bromine, iodine); mono- or di- C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, dimethylamino and diethylamino); C_{1-4} acylamino (e.g. formylamino and acetylamino); hydroxyl; carboxyl; nitro; C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy and butoxy); C_{1-6} alkyl-carbonyloxy (e.g. acetoxy and ethyl carbonyloxy)), halogen (e.g. fluorine, chlorine, bromine and iodine), and such optionally substituted groups bonded through nitrogen atom as described below. Number of the substituents ranges from 1 to 6, preferably 1 to 3.

Examples of the groups bonded through nitrogen atom shown by R^1, R^2, R^7, R^9 and R^{17}, include, each

optionally substituted, groups shown by

$$-NR^{22}R^{23}$$

wherein R^{22} is hydrogen, alkyl, cycloalkyl, aryl, heterocyclic groups and -SOp- (p is 1 to 2) and R^{14} is hydrogen or alkyl, and heterocyclic groups bonded through a nitrogen atom (e.g. 1H-1-pyrrolyl, 1-imidazolyl, pyrazolyl, indolyl, 1H-1-indazolyl, 7-purinyl, 1-pyrrolidinyl, 1-pyrrolinyl, 1-imidazolidinyl, pyrazolidinyl, piperazinyl, pyrazolidinyl, 4-morpholinyl and 4-thiomorpholinyl). Said alkyl, cycloalkyl, aryl and a heterocyclic group are the same meaning as described in the above.

Examples of the substituents, which the group bonded through nitrogen atom may have, include C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl), C_{2-6} alkenyl (e.g. vinyl, 1-methylvinyl, 1-propenyl and allyl), C_{2-6} alkynyl (e.g. ethynyl, 1-propynyl and propargyl), C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C_{5-7} cycloalkenyl (e.g. cyclopentenyl and cyclohexenyl), C_{7-11} aralkyl (e.g. benzyl, α-methylbenzyl and phenethyl), C_{6-14} aryl (e.g. phenyl and naphthyl), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy), C_{6-14} aryloxy (e.g. phenoxy), C_{1-6} alkanoyl (e.g. formyl, acetyl, propionyl, n-butyryl and isobutyryl), C_{6-14} aryl-carbonyl (e.g. benzoyl), C_{1-6} alaknoyloxy (e.g. formyloxy, acetyloxy, propionyloxy and iso-butyryloxy), C_{6-14} aryl-carbonyloxy (e.g. benzoyloxy), carboxyl, C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl and tert-butoxycarbonyl), carbamoyl group, N-mono- C_{1-4} alkylcarbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl,

N-isopropylcarbamoyl and N-butylcarbamoyl), N,N-di- C_{1-4} alkylcarbamoyl (e.g. N,N-di methylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl and N,N-dibutylcarbamoyl), cyclic aminocarbonyl (e.g. 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl and morpholinocarbonyl), halogen (fluorine, chlorine, bromine and iodine), mono- or tri-halogeno- C_{1-4} alkyl (e.g. chloromethyl, dichloromethyl, trifluoromethyl and trifluoroethyl), oxo group, amidino, imino group, amino, mono- or di C_{1-4} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, diisoopropylamino and dibutylamino), 3- to 6-membered cyclic amino group containing, besides the carbon atom and one nitrogen atom, 1 to 3 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom (e.g. aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, dihydropyridyl, N-methylpiperazinyl and N-ethylpiperazinyl), C_{1-6} alkanoylamino (e.g. formamide, acetamide, trifluoroacetamide, propionylamindo, butyrylamido and isobutyrylamido), benzamido, carbamoylamino, N- C_{1-4} alkylcarbamoylamino (e.g. N-methylcarbamoylamino), N-ethylcarbamoylamino, N-propylcarbamoylamino, N-isopropylcarbamoylamino and N-butylcarbamoylamino), N,N-di- C_{1-4} alkylcarbamoylamino (e.g. N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino and N,N-dibutylcarbamoylamino), C_{1-3} alkylenedioxy (e.g. methylenedioxy and ethylenedioxy), $-B(OH)_2$, hydroxyl, epoxy (-O-), nitro, cyano, mercapto, sulfo, sulfino, phosphono, dihydroxyboryl, sulfamoyl, C_{1-6} alkylsulfamoyl, (e.g. N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl

and N-butyl sulfamoyl), di- C_{1-6} alkylsulfamoyl (e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl and N,N-dibutylsulfamoyl), C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio and tert-butylthio), phenylthio, C_{1-6} alkylsulfinyl (e.g. methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl), phenylsulfinyl, C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl and butylsulfonyl), and phenylsulfonyl. The number of the substituents ranges from 1 to 6, preferably 1 to 3.

Examples of the groups bonded through oxygen atom shown by R^1, R^2 and R^7, include hydroxyl, each optionally substituted, alkoxyl, cycloalkoxy, aryloxy, aralkyloxy and heterocyclic hydroxyl groups. The alkyl, cyloalkyl, aryl, aralkyl and heterocyclic groups, in the said alkoxy, cycloalkoxy, aryloxy, aralkyloxy and heterocyclic hydroxyl groups, are of the same meaning as above.

The substituents, which the said oxygen atom may have, are of the same meaning as that of the above-mentioned groups bonded through nitrogen atom.

Examples of the groups bonded through sulfur atom, shown by R^1, R^2, R^7 and R^{12}, include mercapto, alkylthio, cycloalkylthio, arylthio, aralkylthio and heterocyclic thio groups. The alkyl, cycloalkyl, aryl, aralkyl and heterocyclic groups, in the said alkylthio, cycloalkylthio, arylthio, aralkylthio and heterocyclic thio groups, are of the same meaning as defined above.

The substituents, which the said sulfur atom may have, are of the same meaning as that of the substituents which the above-mentioned optionally substituted groups bonded through nitrogen atom may have.

Examples homocyclic groups in the optionally substituted homocyclic groups shown by R^3 include 3- to

7-membered cyclic hydrocarbon groups consisting of only carbon atoms, for example, C_{3-7} cycloalkane (e.g. cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane) and C_{3-7} cycloalkene (e.g. cyclopropene, cyclobutene, cyclopentene, cyclohexene and cycloheptene).

Examples of the substituents which the said homocyclic groups may have, include C_{1-15} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and pentadecyl), C_{3-10} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C_{2-10} alkenyl (e.g. vinyl, allyl, 2-methylallyl, 2-butenyl, 3-butenyl and 3-octenyl), C_{2-10} alkynyl (e.g. ethynyl, 2-propynyl and 3-hexynyl), C_{3-10} cycloalkyl (e.g. cyclopropenyl, cyclopentenyl and cyclohexenyl), C_{6-10} aryl (e.g. phenyl and naphthyl), C_{1-19} aralkyl, (e.g. benzyl, phenylethyl and trityl), nitro, hydroxyl, mercapto, oxo, thioxo, cyano, carbamoyl, carboxyl, C_{1-5} alkoxy-carbonyl (e.g. methoxycarbonyl and ethoxycarbonyl), sulfo, halogen (e.g. fluorine, chlorine, bromine and iodine), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy and t-butoxy), C_{6-10} aryloxy (e.g. phenoxy), C_{1-6} alkylthio (e.g. methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio and t-butylthio), C_{6-10} arylthio (e.g. phenylthio), C_{1-6} alkylsulfinyl (e.g. methylsulfinyl and ethylsulfinyl), C_{6-10} arylsulfinyl (e.g.phenylsulfinyl), C_{1-6} alkylsulfonyl (e.g. methylsulfonyl and ethylsulfonyl), C_{6-10} arylsulfonyl (e.g. phenylsulfonyl), amino, C_{1-6} acylamino (e.g. acetylamino and propylamino), mono- or di- C_{1-4} alkylamino (e.g. methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, dimethylamino and diethylamino), C_{3-8} cycloalkylamino

(e.g. cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino), C_{6-10} arylamino (e.g. anilino), C_{1-6} aralkyl (e.g. formyl, acetyl and hexanoyl), C_{6-10} aryl-carbonyl (e.g. benzoyl), and 5- to 6-membered heterocyclic group containing, besides carbon atom, 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen (e.g. 2- or 3-thienyl, 2- or 3-furyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 1,2,3- or 1,2,4-triazolyl, 1H or 2H-tetrazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidyl, 3- or 4-pyridazinyl, quinolyl, isoquinolyl and indolyl). Number the substituents ranges from 1 to 6, preferably from 1 to 3.

Examples of the above-mentioned optionally substituted heterocyclic groups shown by R^3 include 5- to 8-membered cyclic groups or condensed ring thereof containing, besides carbon atom, 1 to 4 hetero-atoms such as oxygen atom, sulfur atom and nitrogen atom, for example, 5-membered cyclic groups containing, besides carbon atom, 1 to 4 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, as exemplified by 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, and 1H- or 2H-tetrazolyl; 6-membered cyclic groups containing, besides, carbon atom, 1 to 4 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, as exemplified by N-oxido-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido-2-, 4-or 5-pyrimidinyl, thiomorpholinyl, morpholinyl,

oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, piperazinyl, pyranyl, thiopyranyl, 1,4-oxadinyl, 1,4-thiazinyl, 1,3-thiazinyl, piperazinyl, triazinyl, oxotriazinyl, 3- or 4-pyridazinyl, pyrazinyl and N-oxido-3- or 4-pyridazinyl; bicyclic or tricyclic condensed ring groups containing, besides carbon atom, 1 to 4 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, as exemplified by benzofuryl, benzothiazolyl, benzoxazolyl, tetrazolo[1,4-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, benzoimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthaladinyl, quinazolinyl, quinoxalinyl, indolidinyl, quinolidinyl, 1,8-napthylidinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenathridinyl, chromanyl, benzoxadinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

Examples of substituents, which said heterocyclic groups may have, C_{1-6} alkyl (e.g. methyl,ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl), C_{2-6} alkenyl (e.g. vinyl,1-methylvinyl, 1-propenyl and allyl), C_{2-6} alkynyl (e.g. ethynyl, 1-propinyl and propargyl), C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl) and cyclohexyl), C_{5-7} cycloalkenyl (e.g. cyclopentenyl and cyclohexenyl), C_{7-11} aralkyl (e.g. benzyl, α-methylbenzyl and phenethyl), C_{6-14} aryl (e.g. phenyl and naphthyl), C_{1-6} alkoxy (e.g.methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy), C_{6-14} aryloxy (e.g. phenoxy), C_{1-6} alkanoyl (e.g. formyl, acetyl, propionyl, n-butyryl and iso-butyryl), C_{6-14} aryl-carbonyl (e.g. benzoyl), C_{1-6} alkanoyloxy (e.g. formyloxy, acetyloxy, propionyloxy, n-butyryloxy and isobutyryloxy), C_{6-14} aryl-carbonyloxy (e.g. benzoyloxy), carboxyl, C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl,

iso-propoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl and tert-butoxycarbonyl), carbamoyl group, N-mono- C_{1-4} alkylcarbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl and N-butylcarbamoyl), N,N-di- C_{1-4} alkylcarbamoyl (e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl and N,N-dibutylcarbamoyl), cyclic aminocarbonyl (e.g. 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl and morpholinocrbonyl), halogen (fluorine, chlorine, bromine, iodine), mono-, di or tri-halogeno C_{1-4} alkyl (e.g. chloromethyl, dichloromethyl, trifluoromethyl and trifluoroethyl), oxo group,amidino, imino group, amino, mono- or di- C_{1-4} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, diisopropylamino and dibutylamino), 3- to 6-membered cyclic amino group optionally containing, besides carbon atoms and one nitrogen atom, 1 to 3 hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom (e.g. aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl and N-ethylpiperazinyl), C_{1-6} alkanoylamino (e.g. formamido, acetamido, trifluoroacetamido, propionylamido, butylamido and isobutyrylamido), benzamide, carbamoylamino, N- C_{1-4} alkylcarbamoylamino (e.g. N-methylcarbamoylamino, N-ethylcarbamoylamino, N-propylcarbamoylamino, N-isopropylcarbamoylamino and N-butylcarbamoylamino), N,N-di- C_{1-4} alkylcarbamoylamino (e.g.N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino and N,N-dibutylcarbamoylamino), C_{1-3} alkylenedioxy (e.g. methylenedioxy and

ethylenedioxy), $-B(OH)_2$, hydroxyl, epoxy (-O-), nitro, cyano, mercapto, sulfo, sulfino, phosphono, dihydroxyboryl, sulfamoyl, C_{1-6} alkylsulfamoyl (e.g. N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl and N-butylsulfamoyl), di- C_{1-6} alkylsulfamoyl (e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl and N,N-dibutylsulfamoyl), C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio and tert-butylthio), phenylthio, C_{1-6} alkylsulfinyl (e.g. methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl), phenylsulfinyl, C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl and butylsulfonyl) and phenylsulfonyl. Number of the substituents ranges from 1 to 6, preferably 1 to 3.

As the ester group in the optionally esterified carboxyl group shown by R^4, mention is made of, for example, alkyl, cycloalkyl, aryl and heterocyclic groups, and these are of the same meaning as defined above.

Examples of the amidated carboxyl groups shown by R^4 include groups shown by $-CONR^{22}R^{23}$ (wherein R^{22} and R^{23} are of the same meaning as defined above).

As the lower alkyl in the lower alkyl substituted by a group bonded through a sulfur atom shown by R^4, mentioned is made of, for example, C_{1-6} alkyl such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl and the like. The group bonded through a sulfur atom is as the same meaning as defined above.

The lower alkyl in the lower alkyl substituted by an optionally substituted hydroxyl shown by R^4 is the same meaning as defined above.

As substituents on the lower alkyl group, having optionally substituted hydroxyl, shown by the above-

mentioned R^4, use is made of, for example, C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl and tert-butyl) optionally having 1 to 4 substituents selected from halogen (e.g. chlorine, bromine and fluorine), C_{6-10} aryl (e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenylethyl) and nitro; C_{6-10} aryl (e.g. phenyl and naphthyl) optionally having 1 to 4 substituents selected from halogen (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and n-propyl), C_{1-10} aryl (e.g. phenyl and naphthyl); C_{7-12} aralkyl (e.g. benzyl, phenylethyl and naphtylmethyl) optionally having 1 to 4 substituents selected from halogen, (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and and n-propyl), C_{6-10} aryl (e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenethyl) and nitro; C_{1-6} alkyl-carbonyl (e.g. acetyl and propionyl) optionally having 1 to 3 substituents selected from formyl, halogen (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and n-propyl), C_{6-10} aryl(e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenylethyl) and nitro; C_{6-10} aryloxy-carbonyl (e.g. phenyloxycarbonyl and naphthyloxycarbonyl) optionally having 1 to 4 substituents selected from halogen (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and n-propyl), C_{6-10} aryl(e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenylethyl)and nitro; C_{6-10} aryl-carbonyl (e.g. benzoyl and naphthylcarbonyl) optionally having 1 to 4 substituents selected from halogen (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and n-propyl), C_{6-10} aryl (e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenylethyl) and nitro; C_{7-12} aralkyl-carbonyl (e.g.benzylcarbonyl and phenethylcarbonyl) optionally having 1 to 4

substituents selected from halogen (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and n-propyl), C_{6-10} aryl (e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenethyl) and nitro; and pyranyl or furanyl, tri (C_{1-4} alkyl) silyl (e.g. trimethylsilyl and triethylsilyl) optionally having 1 to 4 substituents selected from halogen (e.g. chlorine, bromine and fluorine), C_{1-6} alkyl (e.g. methyl, ethyl and n-propyl), C_{6-10} aryl (e.g. phenyl and naphthyl), C_{7-12} aralkyl (e.g. benzyl and phenethyl) and nitro.

As the hydrocarbon residue in the carbonyl group optionally substituted by the hydrocarbon residue, shown by R^4, mention is made of, for example, saturated or unsaturated hydrocarbon residues having up to 25 carbon atoms. Examples of them include alkyl (e.g. C_{1-8} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl), cycloalkyl (e.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl and cyclohexyl), alkoxyalkyl (e.g. C_{1-3} alkoxy-C_{1-6} alkyl such as methoxymethyl, ethoxymethyl, ethoxybutyl and propoxyhexyl), alkenyl (e.g. C_{2-6} alkenyl such as vinyl,butenyl, butadienyl and hexatrienyl), aryl (e.g. C_{6-14} aryl such as phenyl, naphthyl and antracenyl) and aralkyl (e.g. C_{7-20} aralkyl such as benzyl, benzhydrile and trityl).

The optionally substituted 5 to 7 membered heterocyclic group having as a group capable of constituting the ring, carbonyl, thiocarbonyl, an optionally oxidized sulfur atom or a group convertible them, shown by R^6, in the same meaning as defined on page 5, line 45 to page 9, line 35 of EP-A-0520423.

Examples of the anion-forming groups or groups convertible to amino, shown by the above-mentioned R^6, include carboxyl, C_{1-4} alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic acid amido,

phosphoric acid group and sulfonic acid group. As the spacer group shown by V, mention is made of, for example, -(C=O)-, -O-, -S-, -NH-, -(C=O)-NH-, $-O-CH_2-$, $-S-CH_2-$ and -CH=CH-.

The optionally substituted aromatic hydrocarbon residue optionally containing a hetero atom and the optionally substituted heterocyclic group, shown by the ring Z, is the same meaning as defined on page 5, lines 38 to 44 of EP-A-0520423.

As the aryl shown by R^{11} or in the optionally substituted aryl shown by R^{12} and R^{14}, mention is made of, for example, mono cyclic- or condensed polycyclic-aromatic hydrocarbon residues. Preferable example of them includes C_{6-14} aryl such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and the like. Among these, phenyl, 1-naphthyl and 2-naphthyl are more preferable.

The number of substituent is one or more, preferably one to three. Examples of the substituents include, C_{1-3} alkyl (e.g. methyl, ethyl, propyl), C_{2-4} alkenyl (e.g. vinyl, allyl, 2-buetnyl), C_{3-4} alkynyl (e.g. propargyl, 2-butynyl), C_{3-7} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), aryl (e.g. phenyl, naphthyl), 5- to 9-membered aromatic heterocyclic group having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g. furyl, thienyl, pyrrolyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl), 5- to 9-membered nonaromatic heterocyclic group having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g. oxiranyl, azetidinyl, oxethanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazynyl), C_{7-10} aralkyl (e.g. benzyl, phenethyl), amino, N-monosubstituted amino (e.g. N-C_{1-6} alkyl amino such as methylamino, ethylamino, propylamino), N,N-

disubstituted amino [e.g. N,N-di(C_{1-6} alkyl) amino such as dimethylamino, diethylamino], amidino, acyl (e.g. C_{1-8} alkyl-carbonyl such as acetyl, propionyl, butyryl; C_{6-14} aryl-carbonyl such as benzoyl; C_{7-12} aralkyloxy-carbonyl such as benzyloxycarbonyl), carbamoyl, N-monosubstituted carbamoyl [e.g. N-(C_{1-6}) alkyl)carbamoyl such as methylcarbamoyl, ethylcarbamoyl, ethylcarbamoyl, propylcarbamoyl], N,N-disustituted carbamoyl [e.g. N,N-di(C_{1-6} alkyl)carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl], sulfamoyl, N-monosubstituted sulfamoyl [e.g. N-(C_{1-6} alkyl)sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl], N,N-disubstituted sulfamoyl [e.g. N,N-di(C_{1-6} alkyl)sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl], carboxyl, C_{1-3} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl), hydroxyl, C_{1-3} alkoxy (e.g. methoxy, ethoxy, propoxy) which may have a substituent (e.g. C_{1-3} alkyl, halogen, C_{1-3} alkylthio, hydroxyl), C_{2-4} alkenyloxy (e.g. vinyloxy, allyloxy), cycloalkyloxy (e.g. C_{3-7} cycloalkyloxy such as cyclopropyloxy, cyclobutyloxy), aralkyloxy (e.g. C_{7-10} aralkyloxy such as benzyloxy), aryloxy (e.g. phenyloxy, naphthyloxy), mercapto, C_{1-3} alkylthio (e.g. methylthio, ethylthio, propylthio), aralkylthio (e.g. C_{7-10} aralkylthio such as benzylthio), arylthio (e.g. phenylthio, naphthylthio), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, propylenedioxy), sulfo, cyano, azide, nitro, nitroso, halogen *fulorine, chlorine, bromine iodine), and the like.

As the aralkyl in the optionally substituted aralkyl shown by R^{12}, mention is made of, for example, aryl-alkyl. The aryl is of the same meaning as defined above. Examples of the alkyl include C_{1-6} alkyl such as methyl, ethyl, propyl, butyl, pentyl, hexyl. The substituents are of the same meaning as defined in the

substituents which the above aryl, shown by R^{12}, may have.

As the cycloalkyl in the optionally substituted cycloalkyl shown by R^{11} and R^{12}, mention is made of, for example, C_{3-10} cycloalkyl and C_{3-10} bicycloalkyl. The preferable examples of them include cyclolprolyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2,2,1]heptyl, bicyclo[2,2,2]octyl, bicyclo[3,2,1]octyl, bicyclo[3,2,1]nonyl, bicyclo[4,2,1]nonyl, bicyclo[4,3,1]decyl. Among these, cyclopentyl and cyclohexyl are more preferable. The substituents are of the same meaning as definede in the substituents which aryl, shown by R^{12}, may have.

As the heterocyclic group in the optionally substituted heterocyclic group shown by R^{11}, mention is made of, for example, 5- to 13-membered aromatic heterocyclic group having one to four hetero atom(s) sedected from an oxygen atom, a sulfur atom and a nitrogen atom; or saturated or unsaturated non-aromatic heterocyclic group.

Examples of the aromatic heterocyclic group include an aromatic monocyclic heterocyclic group (e.g. furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl), an aromatic condensed-ring heterocyclic group {e.g. benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indoryl, isoindoryl, 1H-indazolyl, benzoimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-binzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-

carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyridazinyl, 1,2-4-tiazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl}.

Examples of the non-aromatic heterocyclic group include oxylanyl, azetizinyl, oxethanyl, thiethanyl, pyrrolidinyl, tetrahydrofuranyl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl.

The heterocyclic group may have one or more substituents, preferably one to three substituents. The substituents are of the same meaning as defined in the optionally substituted aryl shown by R^{12}.

As the substituents in the optionally substituted carboxyl group shown by Q, mention is made of, for example, alkyl, cycloalkyl, aryl, aralkyl, a heterocyclic group. These are of the same meaning as defined above.

As the lower alkylenedioxy shown by Q, mention is made of, for example, C_{1-6} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, propylenedioxy, 2,2-dimethylmetylenedioxy).

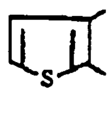
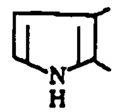
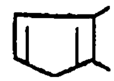
As the lower alkyl shown by R^{11}, mention is made of, for example, C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl).

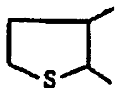
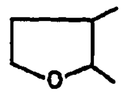
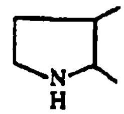
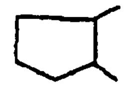
As the optionally substituted amino group shown by R^{13}, mention is made of, for example, a group of the formula: $-NR^{22'}R^{23'}$ wherein $R^{22'}$ is an optionally substituted aryl, an optionally substituted heterocyclic group;
$R^{23'}$ is hydrogen, an optionally substituted alkyl).

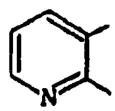
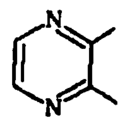
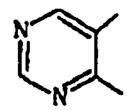
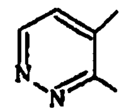
The optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl and optionally substituted heterocyclic group are of the same meaning as defined above.

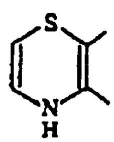
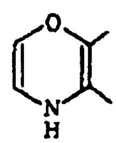
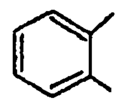
As the spacer group shown by the symbol "A", mention is made of, fro example, C_{1-4} alkylene (e.g. methylene, ethylene), C_{2-6} (e.g. vinylene, butadienylene); a group of the formula: $-(CH_2)cNR^{24}$-in which c is 0 to 3, R^{24} is hydrogen, C_{1-6} alkyl (e.g. methyl, ethyl, butyl); a group of the formula: -CO-; a group of the formula: $-CONR^{22}-$ in which R^{22} is of the same meaning as defined above; -O-; -S-; a group of the formula: $-NR^{22}S(O)e-$ in which e is 0 to 2, R^{22} is of the same meaning as defined above.

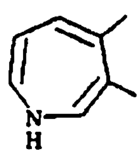
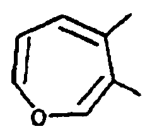
Preferable example of the homo or hetero 5- to 7-membered ring group (ring W') in the optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5- to 7-membered ring group (ring W') and a homo or hetero 5- to 7-membered ring group (ring Y') includes a homo or hetero 5- or 6-membered ring group, more preferably a hetero 5- or 6-membered cyclic group. The concrete examples of the ring W' include ring groups of the formulae:

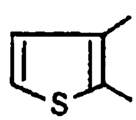
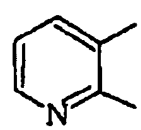
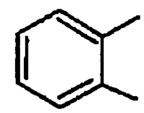
   

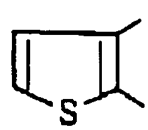
  

  etc.

Among these cyclic groups, those of the formulae

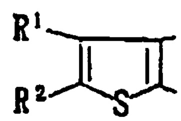
  

are preferable. Further, the cyclic group of the formula



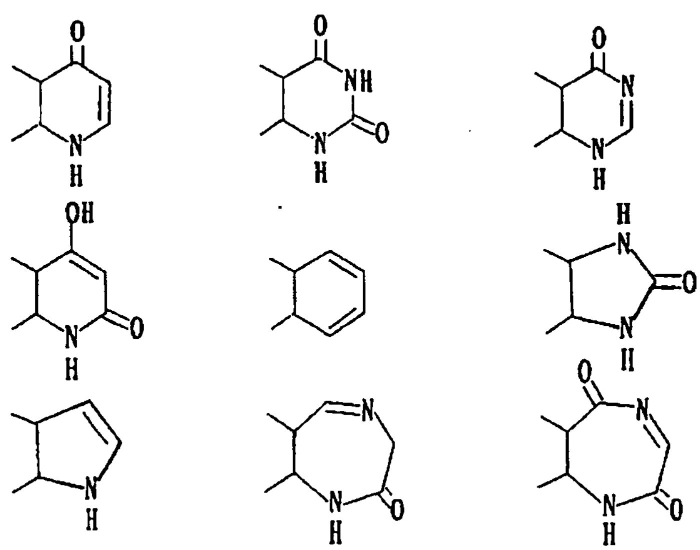
is especially preferable.

Most preferable example of the said W ring is that of the formula

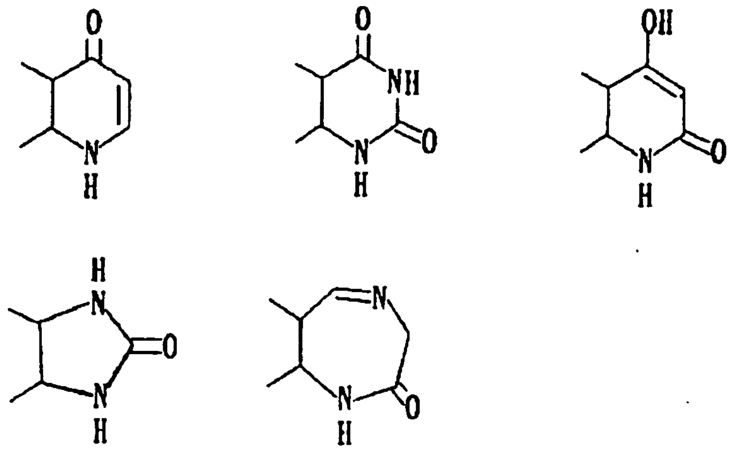


wherein R^1 and R^2 are of the same meaning as defined above.

Preferable example of the homo or hetero 5- to 7-membered ring group (ring Y′) in the optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5- to 7-membered ring group (ring W′) and a homo or hetero 5- to 7-membered ring group (ring Y′) includes a homo or hetero 6-membered ring group, more preferably a hetero 6-membered cyclic group. The concrete examples of the ring W′ include ring groups of the formulae:

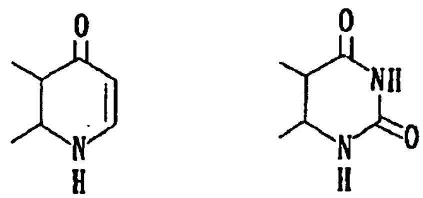


Among these cyclic groups, those of the formulae:



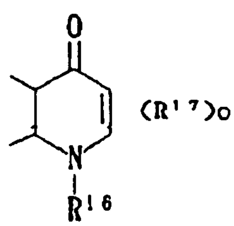
are preferable.

Further, the cyclic groups of the formulae:



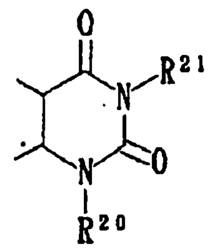
are more preferable.

More preferable examples of the said Y' ring is a ring group of the formula:



wherein R^{16} is an optionally substituted hydrocarbone residue, R^{17} is hydrogen, or a group bonded through a carbon atom, a nitrogen atom, oxygen atom or sulfur atom, o is 1 or 2;

or a ring group of the formula:



wherein R^{20} and R^{21} are each independently hydrogen, an optionally substituted hydrocarbon residure.

Examples of the hydrocarbon residues in the optionally substituted hydrocarbon residues shown by R^{16}, R^{20} and R^{21} include the alkyl, cycloalkyl, aryl and aralkyl described in the foregoing.

Examples of the substituents, which the said hydrocarbon residues may optionally have, include those optionally having 1 to 5 substituents selected from, for example, nitro, hydroxyl, oxo, thioxo, cyano, carbamoyl, carboxyl, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl and ethoxycarbonyl), sulfo, halogen (fluorine, chlorine, bromine and iodine), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, 2-butoxy and t-butoxy), C_{6-12} aryloxy (e.g.phenoxy), halogeno C_{6-16} aryl (e.g. o-, m- or p-chlorophenoxy, and o-, m- or p-bromophenoxy), C_{1-6} alkylthio (e.g. methylthio, ethylthio, n-propiothio, isopropylthio, n-butylthio and t-butylthio), C_{6-12} arylthio (e.g. phenylthio), C_{1-6} alkylsulfinyl (e.g. methylsulfinyl and ethylsulfinyl), C_{1-6} alkylsulfonyl (e.g. methylsulfonyl and ethylsulfonyl), amino, C_{1-6} acylamino (e.g. formylamino, acetylamino and propylamino), mono- or di- C_{1-4} alkylamino (e.g. methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, dimethylamino and diethylamino), C_{1-6} acyl (e.g.formyl, acetyl and hexanoyl), C_{6-12} arylcarbonyl (e.g. benzoyl), 5- or 6-membered heterocyclic groups

containing, besides carbon atoms, 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen, as exemplified by 2- or 3-thienyl, 2- or 3-furyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 1,2,3- or 1,2,4-triazolyl, 1H or 2H-tetrazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidyl, 3- or 4-pyridazininyl, quinolyl, isoquinolyl and indolyl, and C_{1-10} haloalkyl (e.g. difluoromethyl, trifluoromethyl, trifluoroethyl and trichloroethyl), and, in the case of the hydrocarbon group is cycloalkyl, cycloalkenyl, aryl or aralkyl group, C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl and butyl). The number of substituents ranges from 1 to 6, preferably 1 to 3.

The group bonded through a carbon atom, a nitrogen atom, an oxygen atom or a sulfur atom shown by R^{17} is of the same meaning as defined above.

R^1 and R^2 are preferably such ones as either one of them being a group of the formula:

$$R^9-(CH_2)m-$$

wherein R^9 is a group bonded through nitrogen atom, and m is an integer of 0 to 3 and the other one being a group represented by the general formula:

$$R^{10}-A-$$

wherein R^{10} is an optionally substituted phenyl group and A is spacer group.

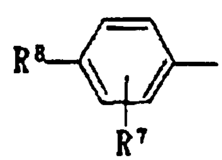
The optionally substituted group, bonded through nitrogen atom, shown by the above-mentioned R^9 is of the same meaning as described above.

Examples of the substituents in optionally substituted phenyl group shown by the above-mentioned R^{10} include halogen (fluorine, chlorine, bromine and iodine), C_{1-8} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl and neopentyl) optionally substituted

with 1 to 3 halogen atoms (fluorine, chlorine, bromine and iodine), C_{1-8} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy) optionally substituted with 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine and iodine), C_{1-8} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio and neopentylthio) optionally substituted with 1 to 3 halogen atoms (fluorine, chlorine, bromine and iodine), C_{1-6} aralkyloxy (e.g. formyloxy, acetoxy and propionyloxy), hydroxyl, carboxyl, C_{1-6} alkoxy-carbonyl (e.g.methoxycarbonyl, ethoxycarbonyl and t-butoxycarbonyl), cyano, nitro, amido, and mono- or di-C_{1-6} alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl and dimethylcarbamoyl). The number of substituents ranges from 1 to 5, preferably 1 to 3.

The spacer groups shown by A is of the same meaning as defined above.

R^3 is preferably a group of the formula:



wherein R^7 is hydrogen or a group bonded through a carbon, nitrogen, oxygen or sulfur atom, and R^8, halogen, nitro, cyano or an optionally substituted aliphatic hydrocarbon residue bonded through oxygen, nitrogen or sulfur atom.

The above-mentioned optionally substituted groups bonded through carbon, nitrogen oxygen or sulfur atom, shown by R^7 are of the same meaning as defined above.

Examples of the optionally substituted aliphatic hydrocarbon residue, in the optionally substituted aliphatic hydrocarbon residue bonded through oxygen, nitrogen or sulfur atom shown by the above-mentioned

R^8, include C_{1-15} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and pentadecyl), C_{3-8} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C_{2-10} alkenyl (e.g. vinyl, allyl, 2-methylallyl, 2-butenyl, 3-butenyl and 3-octenyl), C_{2-10} alkynyl (e.g. ethynyl, 2-propynyl and 3-hexynyl)and C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy and butoxy). Examples of the substituents, which the said hydrocarbon group may have, include nitro, hydroxyl, oxo, thioxo, cyano, carbamoyl, carboxyl, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl and ethoxycarbonyl), sulfo, halogen (fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy and t-butoxy), C_{1-4} alkylthio (e.g. methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio and t-butylthio), amino, C_{1-6} alkanoylamino (e.g. acetylamino and propionylamino), mono- or di- C_{1-4} alkylamino (e.g. methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, dimetylamino and diethylamino), C_{1-4} alkanoyl (e.g. formyl, acetyl and propionyl), 5- or 6-membered heterocyclic groups containing, besides carbon atoms, 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen, which may optionally have 1 to 4 substituents selected from (a) halogen (e.g. fluorine, chlorine, bromine and iodine); and (b) C_{1-4} alkyl (e.g. methyl, ethyl, propyl and isopropyl), as exemplified by 2- or 3-thienyl, 2- or 3-furyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 1,2,3- or 1,2,4-triazolyl, 1H or 2H-tetrazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidyl, 3- or 4-pyridazinyl, quinolyl, isoquinolyl and indolyl,

and C_{1-6} haloalkyl (e.g. difluoromethyl, trifluoromethyl, trifluoroethyl and trichloroethyl). Number of the substituents ranges from 1 to 4, preferably 1 to 3.

R^{11} is preferably a group of the formula:

$-(CH_2)pQ'$

wherein p is an integer of 1 to 3; Q' is aryl which may be substituted by halogen, nitro, cyano, amino, an optionally substituted carboxyl group, lower alkylenedioxy or a group of the formula: $-A-R^{16}$ in which R^{15} is a lower alkyl group, A is of the same meaning as defined above.

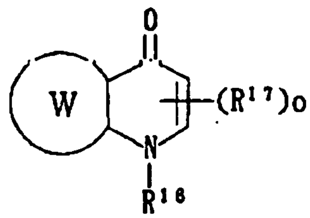
The aryl which may be substituted by halogen, nitro, cyano, amino, the optionally substituted carboxyl group, lower alkylenedioxy or the group of the formula: $-A-R^{16}$, shown by Q', are the of the same meaning as defined above. The lower alkyl group is of the same meaning as defined above.

Q' is preferably an aryl which may be substituted by halogen (fluorine, chlorine, bromine, nitrogen).

R^{13} is preferably an optionally substituted monoaralkylamino. The optionally substituted aralkyl in the optionally substituted monoaralkylamino is of the same meaning as defined above. The aralkyl is preferably benzyl.

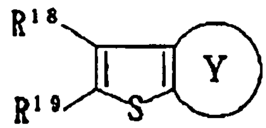
R^{14} is preferably optionally substituted phenyl which is of the same meaning as defined above.

The optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5- to 7-membered ring group and a homo or hetero 5- to 7-membered ring group is preferably a compound of the formula (V):



(V)

wherein ring W, R^{16}, R^{17} and o are the same meaning as defined above; or a compound of the formula (VII):

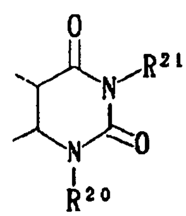


(VII)

wherein R^{18} and R^{19} are each independently an optionally substituted hydrocarbon residue and ring Y is of the same meaning as defined above.

The optionally substituted hydrocarbon residue shown by R^{18} or R^{19} is the same meaning as defined above.

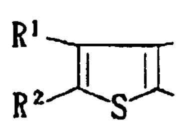
The ring Y is preferably an optionally substituted hetero 5- to 7-membered ring group except for 4-pyridone. More preferably, the ring Y is a ring group of the formula (VIII):



(VIII)

wherein R^{20} and R^{21} are of the same meaning as defined above.

The ring W is preferably a ring group of the formula (VI):



(VI)

wherein R^1 and R^2 are of the same meaning as defined above.

The compounds (I), (II), (VII) and their salts can be produced easily by *per se* known methods, as exemplified by the following production methods 1 to 16.

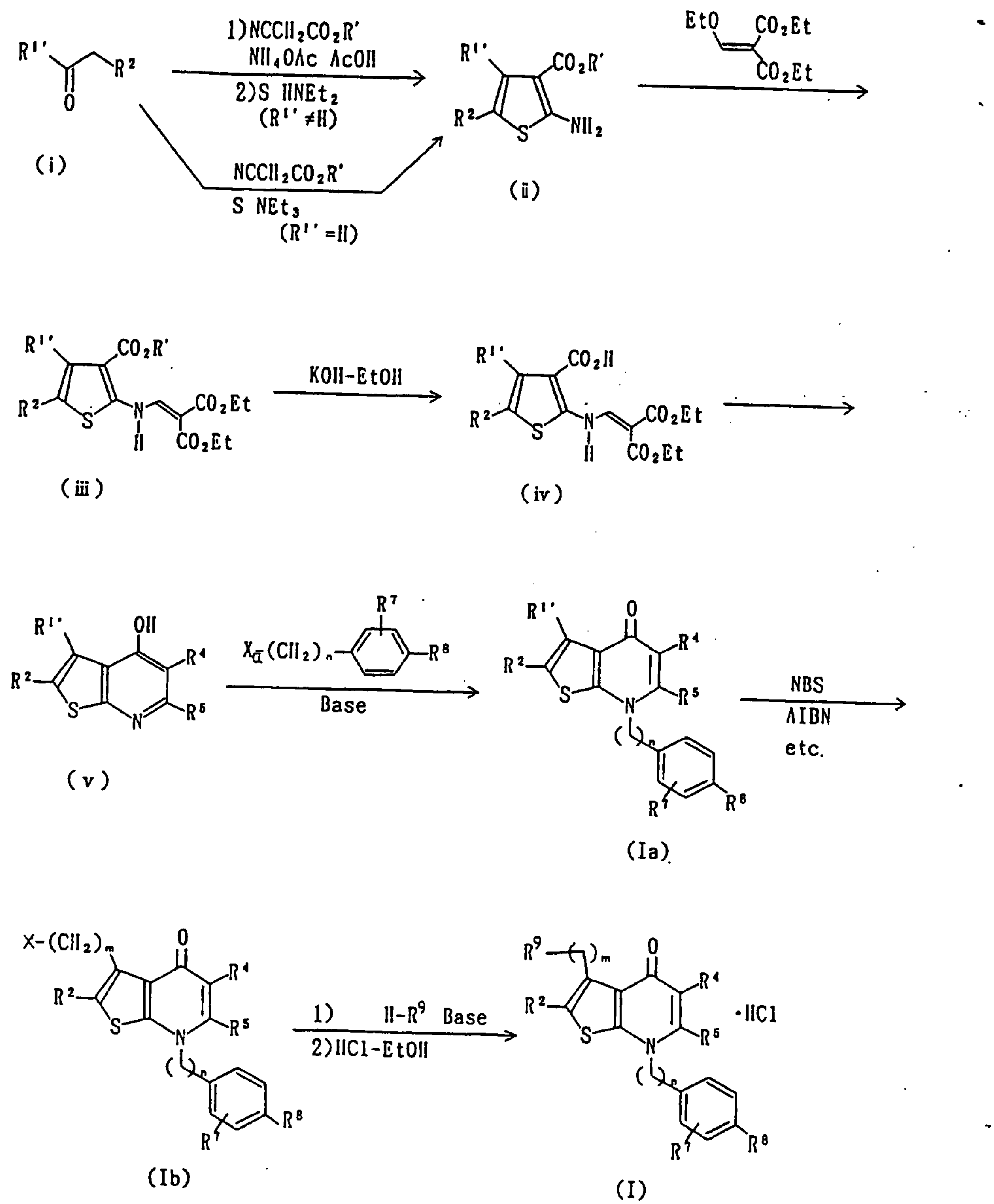
The above-mentioned optionally substituted condensed-bicyclic compound consisting of a homo or hetero 5- to 7-membered ring group and a homo or hetero 5- to 7-membered ring group can be produced by the production methods 1 to 16 or the same production methods thereof.

[Production Method 1]

In accordance with the method disclosed by K. Gewald, E. Schinke and H. Bøttcher, Chem. Ber., 99, 94-100 (1966), an adequate ketone or aldehyde having an active methylene (i) was allowed to react with a cyanoacetic acid ester derivative and sulfur to convert into a 2-aminothiophene derivative (ii). More specifically, in the case of using ketone ($R^{1'}\neq H$), it is subjected to heating under reflux together with a cyanoacetic acid ester derivative, in the presence of acetic acid and ammonium acetate, in a proper solvent such as toluene to give an alkylidene cyanoacetic acid ester derivative, which is then heated in an adequate solvent, for example, ethanol in the presence of sulfur and a base to afford a 2-aminothiophene derivative (ii). And, in the case of using aldehyde ($R^{1'}=H$), it is heated in a proper solvent, for example, dimethylformamide, in the presence of a cyanoacetic acid ester derivative, sulfur and a base to give a 2-aminothiophene derivative (ii). The compound (ii) thus obtained is heated, in accordance with the method disclosed by Kuwata et al. [cf. German Patent 2,435,025], with diethyl ethoxymethylenemalonate to give an adduct (iii). The adduct is stirred in a

solvent, which does not give undesirable effect on the reaction, (e.g. alcohols such as ethanol and methanol), in the presence of a base (e.g. alkali metal hydroxide such as potassium hydroxide and sodium hydroxide) at temperatures ranging from about 10 to 70°C to give carboxylic acid (iv). Then, the carboxylic acid (iv) thus obtained was subjected to ring-closure by heating in polyphosphoric acid ester (PPE) to give a thieno[2,3-b]pyridine derivative (v). The compound (v) is stirred in a solvent, which does not give undesirable effect on the reaction, (e.g. amides such as dimethylformamide and dimethylacetamide), in the presence of a halogenated aralkyl derivative and a base (e.g. an organic base such as pyridine and triethylamine) at temperatures ranging from about 10 to 100°C to give a 4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ester derivative shown by the formula (Ia). Then, the compound (Ia) is stirred together with N-bromosuccinimide (NBS) in a solvent, which does not give undesirable effect on the reaction, (e.g. halogenated hydrocarbons such as carbon tetrachloride and chloroform) in the presence of α, α'-azobisisobutyronitrile, at temperatures ranging from about 30 to 100°C to give a compound (Ib). The compound (Ib) is stirred together with various amines in a solvent, which does not give undesirable effect on the reaction, (e.g. amides such as dimethylformamide and dimethylacetamide, nitrile such as acetonitrile and alcohols such as ethanol) in the presence of a base at temperatures ranging from about 10 to 100°C to produce the compound (I). The production method 1 described above is shown in Scheme 1:

Scheme 1



wherein $R^{1'}$ is hydrogen or an alkyl group, R′ is an alkyl group, X is a leaving group, Xa is halogen, and R^2, R^4, R^5, R^7, R^8, R^9, m and n are of the same meaning as defined in the above.

The alkyl group shown by $R^{1'}$ and R′ is of the same meaning as defined above.

As the leaving group shown by X, mention is made of, for example, a group which is potentially substituted by a nucleophilic reagent such as a hydrocarbon residue having a hetero atom (e.g. an oxygen atom, a sulfur atom, a nitrogen atom) being negatively charged. The preferable examples of the leaving group include halogen (e.g. iodine, bromine chlorine), alkanoyloxy (e.g. acetoxy), alkylsulfonyloxy (e.g. methanesulfonyloxy), alkyl-arylsulfonyloxy (e.g. p-toluenesulfonyloxy).

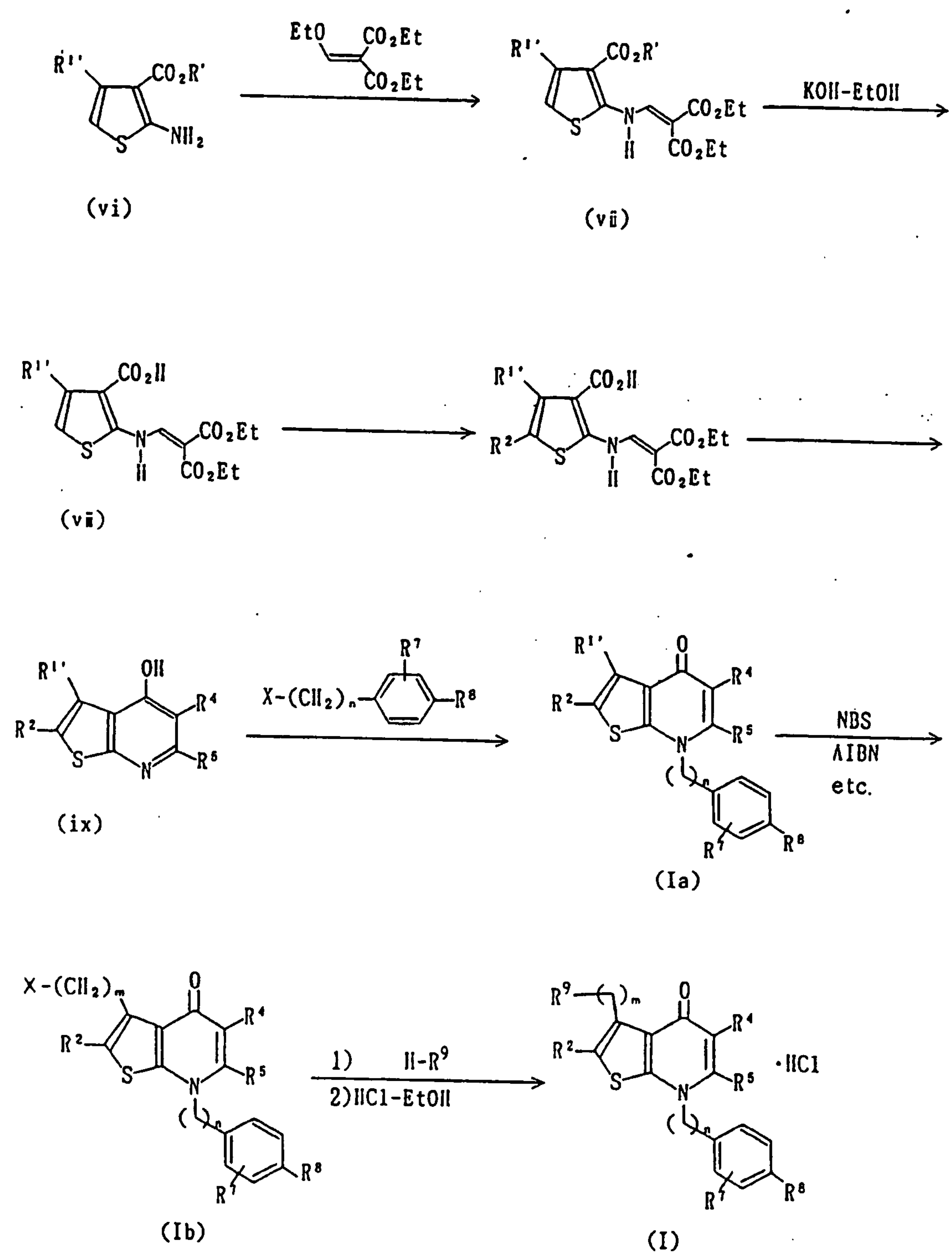
The halogen shown by Xa is fluorine, iodine, chlorine, iodine. Among these, bromine is more preferable.

[Production Method 2]

In substantially the same manner as in [production Method 1], a 2-aminothiophene derivative whose 5-position is unsubstituted (vi), which can be synthesized by the method disclosed by Karl Gewald [K. Gewald, Chem. Ber., 98, 3571-3577 (1965); K. Gewald and E. Schinke, Chem. Ber., 99, 2712-2715 (1966)] is allowed to react with diethyl ethoxymethylene malonate under heating, in accordance with the method disclosed by Kuwata et al. [German Patent 2,435,025], to give an adduct (vii). The adduct is stirred at temperatures ranging from about 10 to 60°C in a solvent, which does not affect adversely on the reaction, (e.g. alcohols such as ethanol and methanol) in the presence of a suitable base (e.g. alkali metal hydroxide such as potassium hydroxide and sodium hydroxide to give carboxylic acid (viii). The compound (viii) is

subjected to various cationoid substitution reactions and, depending on cases, to a suitable change of functional groups to introduce the substituent shown by R^2, which is then subjected to ring-closure reaction under heating in polyphosphoric acid ester (PPE) to give a thieno[2,3-b]pyridine derivative (ix). The compound (ix) is stirred together with a halogenated aralkyl derivative in a solvent, which does not affect adversely on the reaction, (e.g. amides such as dimethylformamide and dimethylacetamide), in the presence of a base, at temperatures ranging from about 10 to 100°C, to give a 4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ester derivative shown by the formula (Iα). As the cationoid substitution reaction, mention is made of, for example, nitration (fuming nitric acid - concentrated sulfuric acid, sodium nitrate - concentrated sulfuric acid), acylation (acid chloride- aluminum chloride), formylation (phosphorus oxychloride - dimethylformamide or N-methylformanilide) and bromination (N-bromosuccinimide, bromine-pyridine). The compound (Iα) is then processed in substantially the same manner as in$_b$ [Production Method 1] to produce the compounds (Ib) and (I). The Production Method 2 is shown in Scheme 2:

Scheme 2


EtO
CO_2Et
CO_2Et
KOH-EtOH
(vi)
(vii)
(viii)
(ix)
(Ia)
(Ib)
(I)
NBS
AIBN
etc.
1) H-R^9
2)HCl-EtOH
·HCl

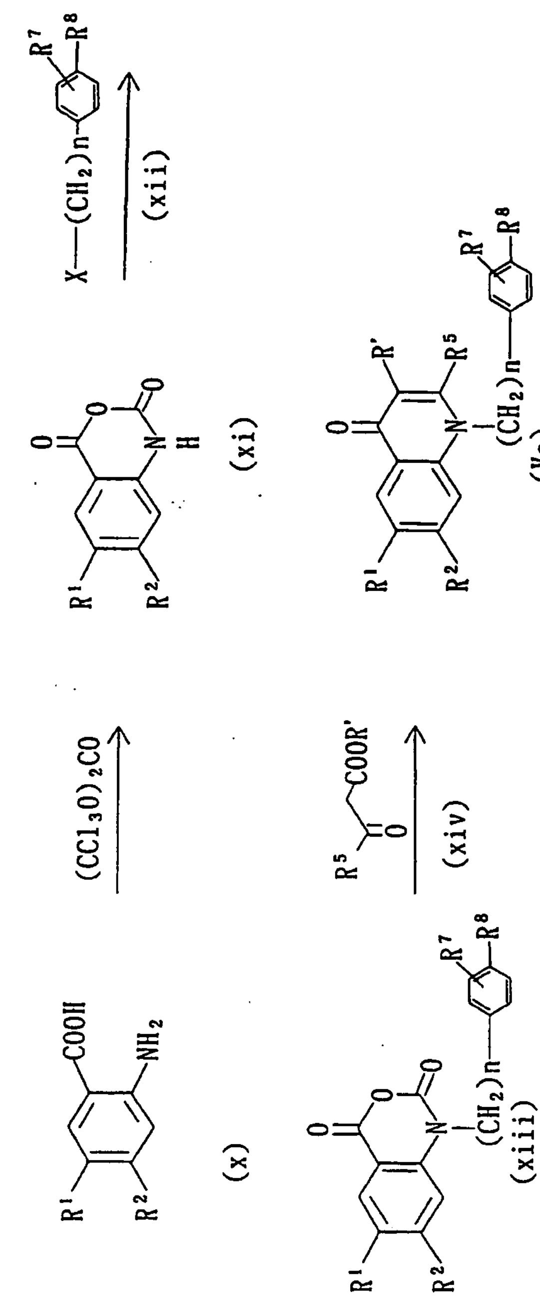
wherein each symbol has the same meaning as defined above.

[Production Method 3]

An alantoic acid derivative (x) is stirred at temperatures ranging from about 30 to 110°C together with an equivalent or an excess amount of triphosgene relative the the compound (x) in a solvent which does not adversely affect on the reaction (e.g. ethers such as tetrahydrofuran and 1,4-dioxane) to give an isatoic acid anhydride derivative (xi). Then, a halogenated derivative shown by the formula (xii) is stirred at temperatures ranging from about 40 to 130°C in a solvent, which does not affect adversely on the reaction, (ethers such as tetrahydrofuran and 1,4-dioxane, aromatic hydrocarbons such as benzene and toluene, amides such as N,N-dimethylformamide and N,N-dimethylacetamide, alkylsulfoxides such as dimethyl sulfoxide), in the presence of a base (e.g. alkali metal carbonate such as potassium carbonate, alkali metal hydride such as sodium hydride and potassium hydride, and alkali metal alkoxide such as potassium-butoxide), to give a substituted derivative (xiii). The derivative (xiii) is allowed to react with an equivalent or a little excess amount (e.g. about 1.1 to 1.5 equivalent) of a β-keto-acid ester derivative (xiv) relative to the compound (xiii) at temperatures ranging from 40 to 110°C in a solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and 1,4-dioxane, aromatic hydrocarbons such as benzene and toluene, amides such as N,N-dimethylformamide and N,N-dimethylacetamide, and alkyl sulfoxide such as dimethyl sulfoxide), in the presence of a base (e.g. alkali metal carbonate such as potassium carbonate, alkali metal hydride such as sodium hydride and potassium hydride, and alkali metal alkoxide such as potassium-butoxide) to give the

compound (Vα). The foregoing production method 3 is shown in Scheme 3:

Scheme 3



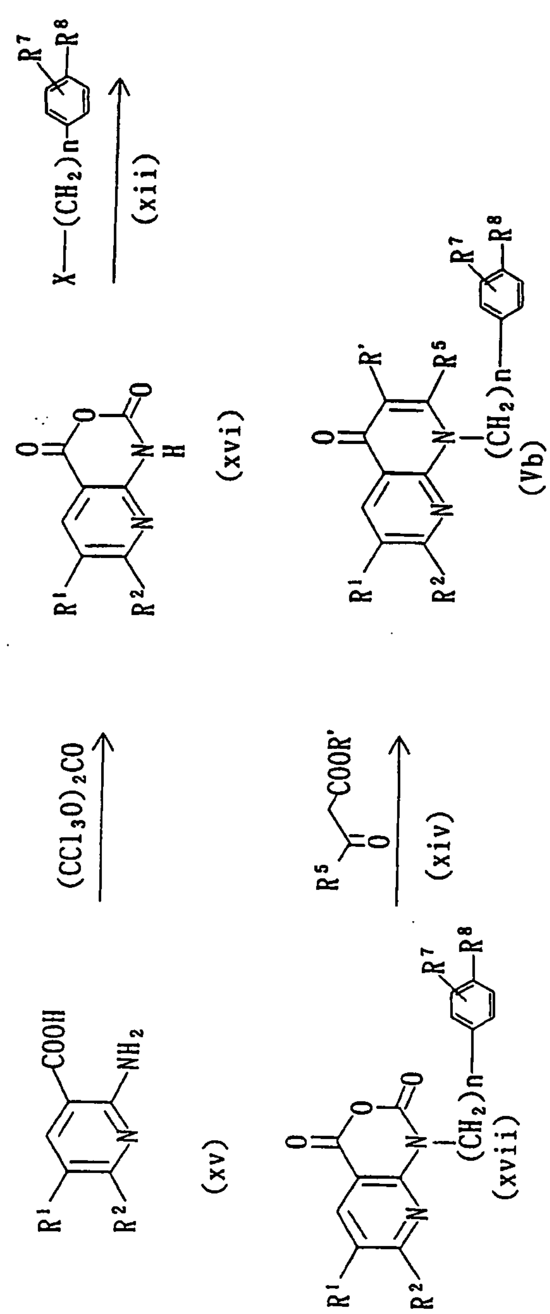
wherein each symbol is of the same meaning as defined above.

[Production Method 4]

A pyridine derivative (xv) is stirred, together with equivalent or an excess amount of triphosgene relative to the compound (xv), in a solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and 1,4-dioxane), at temperatures ranging from about 30 to 110°C to give an acid anhydride derivative (xvi). Then, the halogenated derivative shown by (xii) is stirred in a solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and 1,4-dioxane, aromatic hydrocarbons such as benzene and toluene, amides such as N,N-dimethylformamide and N,N-dimethylacetamide, and alkyl sulfoxides such as dimethyl sulfoxide), at temperatures ranging from about 40 to 130°C in the presence of a base (e.g. alkali metal carbonate such as potassium carbonate, alkali metal hydride such as sodium hydride and potassium hydride, and alkali metal alkoxide such as potassium-butoxide) to give a substituted derivative (xvii). The derivative (xvii) is allowed to react with equivalent or a little excess amount (e.g. 1.1 to 1.5 equivalent) of a β-keto-acid ester derivative (xiv) in a solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and 1,4-dioxane, aromatic hydrocarbons such as benzene and toluene, amides such as N,N-dimethylformamide and M,N-dimethylacetamide, and alkyl sulfoxides such as dimethyl sulfoxide), in the presence of a base (e.g. alkali metal carbonate such as potassium carbonate, alkali metal hydride such as sodium hydride and potassium hydride and alkali metal alkoxide such as potassium-butoxide), at temperatures ranging from about 40 to 110°C, to give the compound (Vb). The

foregoing production method 4 is shown by Scheme 4:

Scheme 4

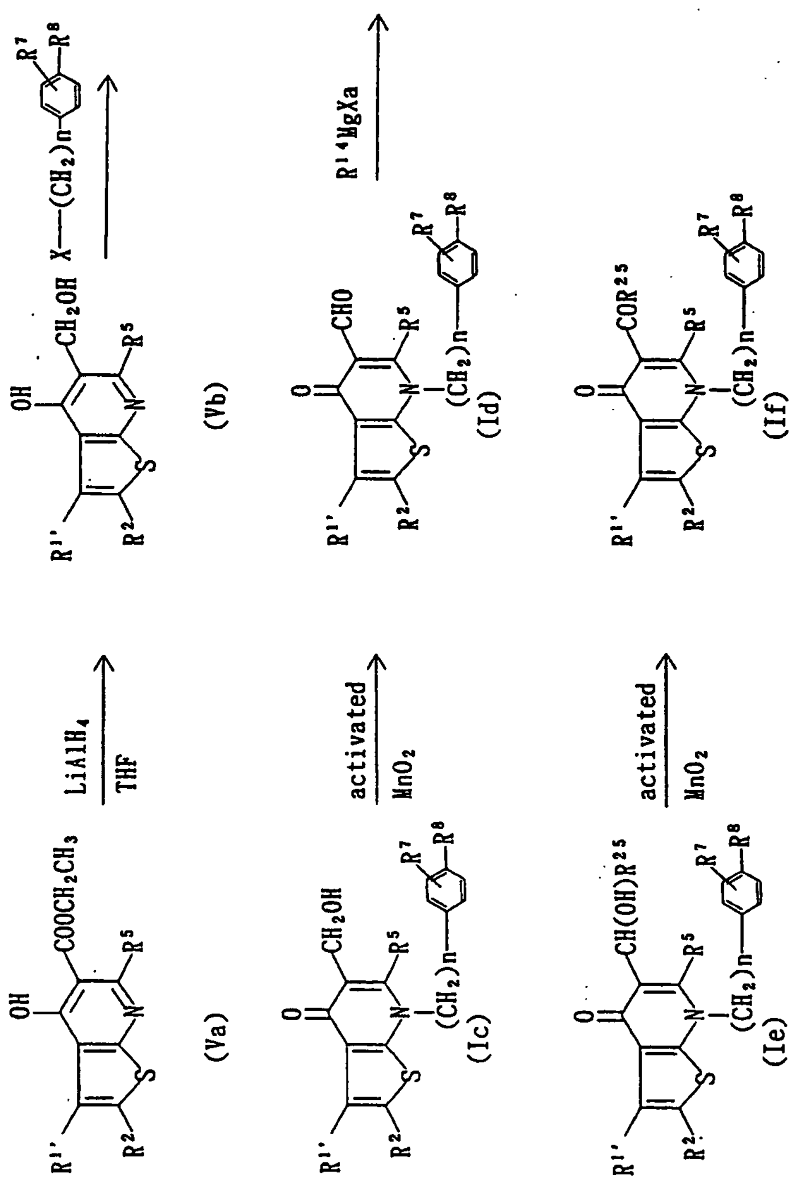


wherein each symbol is of the same meaning as defined above.

[Production Method 5]

In a proper solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran, ethyl ether and dioxane), 4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ester derivative (va) is stirred together with a suitable reducing agent (e.g. lithium aluminum hydride) at temperatures ranging from about 0 to 80°C to give a 4,7-dihydro-thieno[2,3-b]pyridine-4-one derivative shown by the formula (Ic). The said derivative is stirred, together with a suitable oxidizing agent (e.g. manganese dioxide), in a proper solvent (e.g. dichloromethane or chloroform) at temperatures ranging from about 10 to 80°C to give a 5-formyl derivative. The derivative (Id) thus produced is stirred, together with a Grignard's reagent, at temperatures ranging from about 0 to 80°C in a solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and ethyl ether) to give a corresponding secondary alcohol derivative (Ie). The compound (Ie) is stirred, together with a suitable oxidizing agent (e.g. metal oxide such as manganese dioxide), in a proper solvent (e.g. halogenated hydrocarbons such as dichloromethane and chloroform) at temperatures ranging from about 10 to 80°C to give a 5-carbonyl derivative (If). The foregoing production method 5 is shown in Scheme 5:

Scheme 5



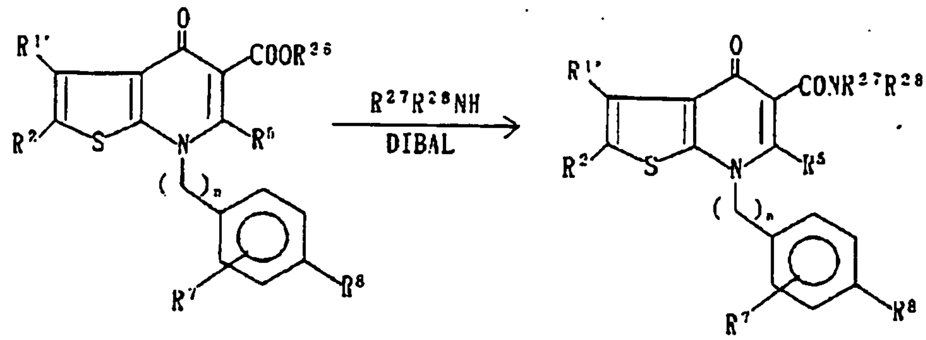
wherein R^{25} is hydrocarbon residue, and other symbols are of the same meaning as defined above.

The hydrocarbon residue shown by the above R^{25} is of the same meaning as the hydrocarbon residue in the carbonyl group optionally substituted with hydrocarbon residue shown by the above-described R^4.

[Production Method 6]

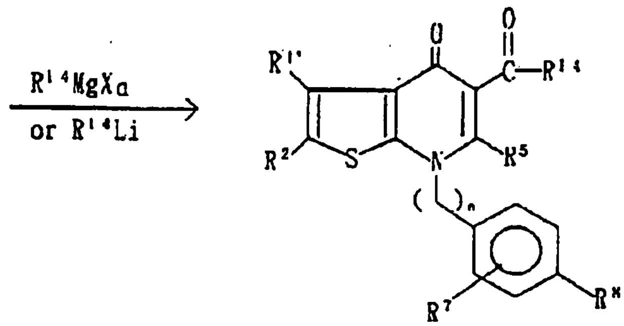
4,7-Dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ester derivative (Iα′) is stirred at temperatures ranging from about 10 to 100°C, together with an aluminum amide derivative previously produced from a proper aluminum reagent [(e.g. trimethyl aluminum and diisobutyl aluminum hydride (DIBAL)] and amine in a suitable solvent, which does not affect adversely on the reaction, (e.g. halogenated hydrocarbons such as dichloromethane and ethers such as tetrahydrofuran, ethyl ether and dioxane), to give a 4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid amide derivative (Iα″). The said derivative (Iα″) is stirred, together with a Grignard's reagent, in a proper solvent, which does not affect adversely on the reaction, (e.g. tetrahydrofuran and ethyl ether) at temperatures ranging from about -78°C to 80°C to give a corresponding ketone derivative (If). The foregoing production method 6 is shown in Scheme 6:

Scheme 6



(Ia')

(Ia'')



(If)

wherein R^{26} is alkyl or aryl; R^{27} and R^{28} are each hydrogen or hydrocarbon residue; and other symbols are of the same meaning as defined above.

The alkyl and aryl shown by the above R^{26} are of the same meaning as defined above.

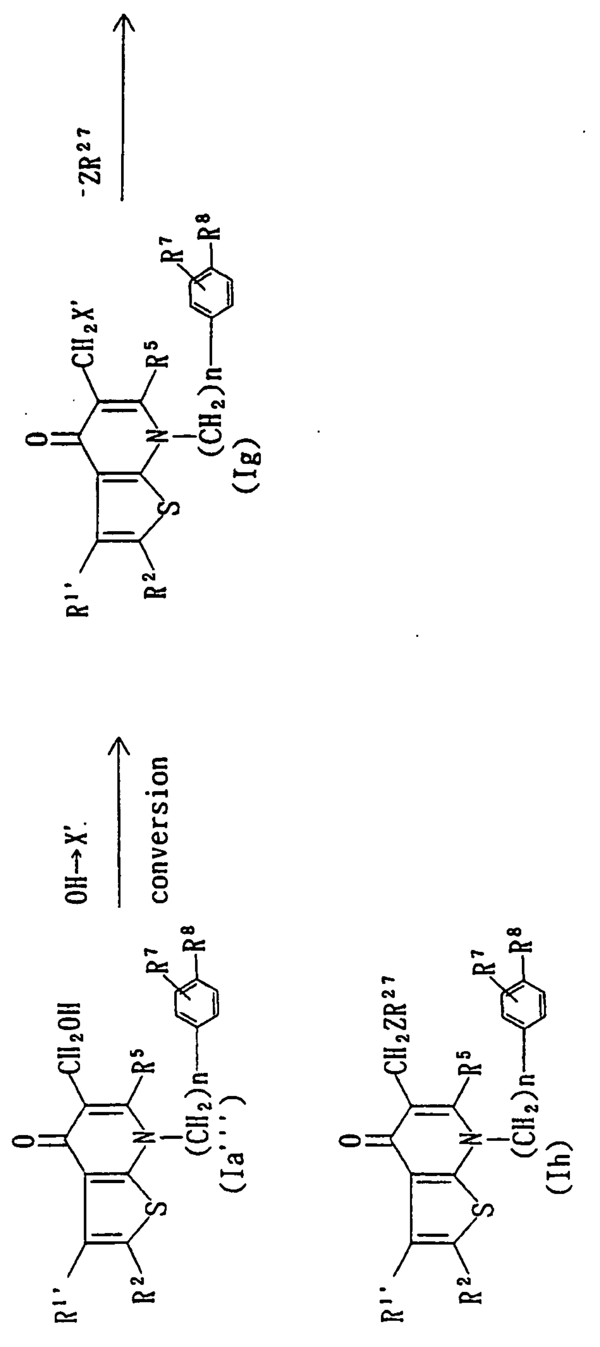
The hydrocarbon residue shown by the above R^{27} and R^{28} has the same meaning as the hydrocarbon residue in the carbonyl group optionally substituted with hydrocarbon residue shown by the above R^4.

[Production Method 7]

In a proper solvent, which does not affect adversely on the reaction, (e.g. halogenated hydrocarbons such as dichloromethane; ethers such as tetrahydrofuran, ethyl ether and dioxane; and

pyridine), a 4,7-dihydro-5-hydroxymethylthieno[2,3-b]pyridine-4-one derivative (Ia''') is stirred together with a suitable halogenating reagent (e.g. thionyl chloride and methanesulfonyl chloride) at temperatures ranging from about 0 to 100°C to give a 4,7-dihydrothieno[2,3-b]pyridine one derivative (Ig). The said derivative (Ig) is stirred, together with a suitable nucleophilic reagent, in a proper solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and ethyl ether; and amides such as dimethylformamide) to give a corresponding 5-substituted derivative (Ih). The above production method 7 is shown in Scheme 7:

Scheme 7



wherein X′ is a leaving group, Z is an oxygen atom, a sulfur atom or a nitrogen atom optionally substituted with hydrocarbon residue, and other symbols are of the same meaning as defined above.

As the leaving group shown by the above X′, mention is made of, for example, groups readily susceptible to substitution reaction by a nucleophilic reagent [e.g. the hydrocarbon residue having a hetero-atom with negative electric charge (e.g. oxygen atom,sulfur atom and nitrogen atom) shown by the above $^{-}YR^{16}$]. More specifically, for example, aralkyloxy (e.g. acetoxy), alkylsulfonyloxy (e.g. methanesulfonyloxy) and alkyl-aryl sulfonyloxy (e.g. p-toluenesulfonyloxy) are mentioned.

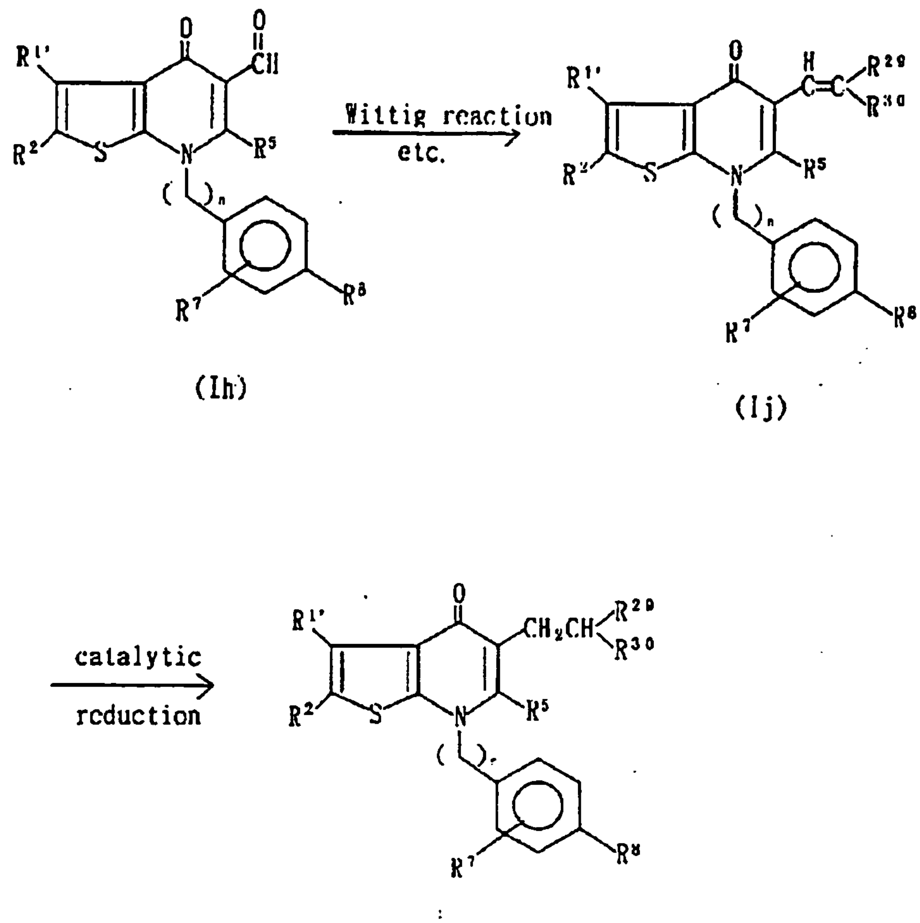
The hydrocarbon residue in the nitrogen atom optionally substituted with hydrocarbon residue mentioned above has the same meaning as defined in reference to the hydrocarbon residue in the carbonyl group optionally substituted with hydrocarbon residue shown by the above-mentioned R^4.

[Production Method 8]

In a proper solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran, ethyl ether and dioxane; and pyridine), 4,7-dihydro-5-formylthieno[2,3-b]pyridine-4-one derivative (Ih) is stirred together with a suitable Wittig reagent at temperatures ranging from about 0 to 100°C to give a 4,7-dihydrothieno[2,3-b]pyridine-4-one derivative (Ij). The said derivative (Ij) is stirred at temperatures ranging from about 10 to 100°C together with a suitable reducing reagent [e.g. hydrogenation using, in hydrogen streams, a catalyst (e.g. palladium-carbon catalyst)] in a proper solvent, which does not affect adversely on the reaction (e.g. alcohols such as ethyl alcohol, esters such as acetic acid ethyl ester, ethers such as tetrahydrofuran, ethyl ether and

dimethylformamide) to give a corresponding 5-substituted derivative (Ik). The above production method 8 is shown in Scheme 8:

Scheme 8



(Ih) (Ij) (Ik)

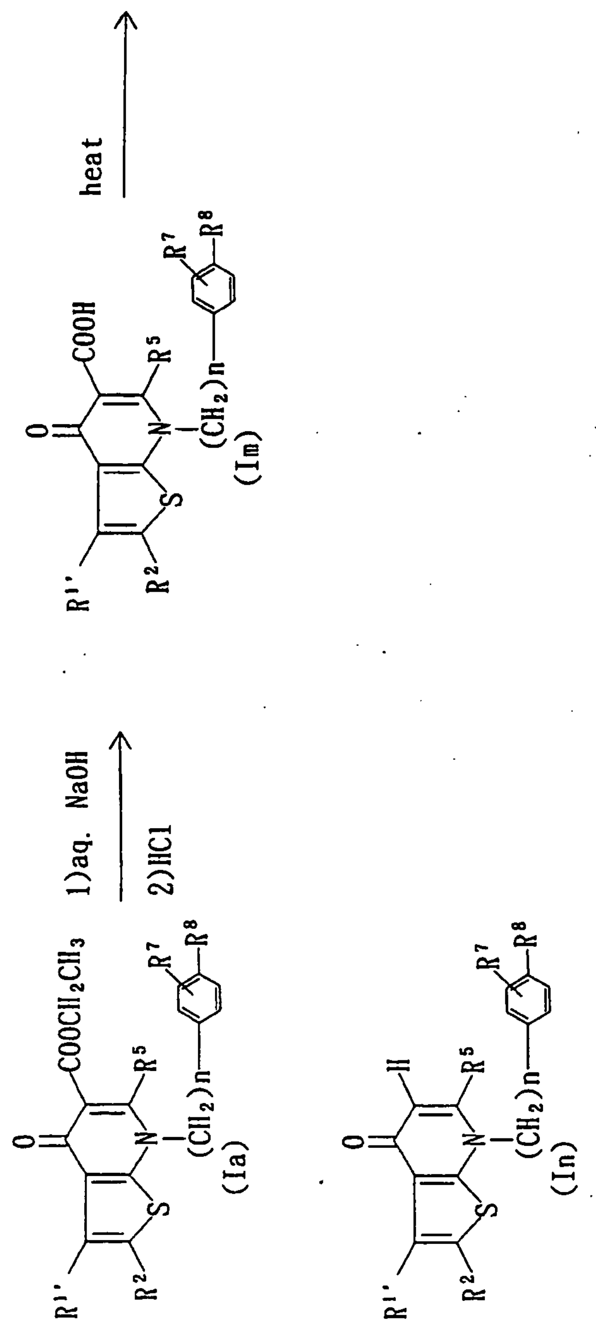
wherein R^{29} and R^{30} are each hydrogen or hydrocarbon residue, and other symbols are of the same meaning as defined above.

The hydrocarbon residue shown by the above-mentioned R^{29} and R^{30} has the same meaning as the hydrocarbon residue in the carbonyl group optionally substituted with the hydrocarbon residue shown by the above-mentioned R^4.

[Production Method 9]

In a proper solvent, which does not affect adversely on the reaction, (e.g. ethers such as tetrahydrofuran and dioxane; and alcohols such as ethyl alcohol), 4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ester derivative (Iα′) is subjected to hydrolysis under stirring at temperatures ranging from about 10 to 100°C by adding an acid (e.g. inorganic acid such as hydrochloric acid) or an alkaline aqueous solution (e.g. 1-4N aqueous solution of alkali metal hydroxide such as sodium hydroxide, potassium hydroxide and lithium hydroxide). The resulting 5-carboxylic acid derivative is heated at temperatures ranging from about 50 to 200°C in a proper solvent, which does not affect adversely on the reaction, to give a corresponding decarboxylated derivative (In). The foregoing production method 9 is shown by Scheme 9:

Scheme 9



wherein each symbol is of the same meaning as defined above.

[Production Method 10]

Starting from the 2-aminothiophene derivative (ii), the urea derivative (II) was produced by, for example, the following method A or B.

1. Method A: The 2-aminothiophene derivative (ii) produced by the method described in Production Method 1 or a salt thereof is allowed to react with an isocyanate derivative. The isocyanate derivative is exemplified by derivatives represented by the formula, R^{12}-NCO (wherein R^{12} is of the same meaning as defined above). The reaction of the compound (ii) or a salt thereof with the isocyanate derivative is conducted in an solvent which does not adversely affect on the reaction (e.g. tetrahydrofuran, pyridine, dioxane, benzene, dichloromethane, 1,2-dichloroethane, toluene, xylene) at temperatures ranging from about 15 to about 130°C. The isocyanate derivative is employed in an amount of about 1 to 5 equivalents, preferably about 1.1 to 2.5 equivalents, relative to 1 equivalent of the compound (ii). The reaction time ranges from several hours to several days, preferably from about 15 minutes to about two days.

2. Method B: Amine [e.g. a compound represented by the formula R^{12}-NH_2 (wherein R^{12} is of the same meaning as defined above)] is subjected to addition reaction to an isocyanate derivative produced by allowing a 2-aminothiophene derivative (ii) or a salt thereof to react with phosgene or an equivalent compound thereof [e.g. diphosgene such as bis(trichloromethyl)carbonate, triphosgene such as trichloromethylchloroformate]. The reaction of the compound (ii) or a salt thereof with phosgene or an equivalent compound thereof is conducted in a solvent which does not affect adversely on the reaction (e.g. dioxane, tetrahydrofuran, benzene,

toluene, xylene, 1,2-dichloroethane, chloroform) at temperatures ranging from about 40 to 120°C. Phosgene or an equivalent compound thereof is employed in an amount ranging from about 0.5 to 2 equivalents, preferably from about 0.9 to 1.1 equivalent). The reaction time ranges from several minutes to several days, preferably from about 15 minutes to about two days. The addition reaction of amine is conducted in a solvent which does not affect adversely on the reaction (e.g. pyridine, tetrahydrofuran, dioxane, benzene, dichloromethane, 1,2-dichloroethane, toluene, xylene) at temperatures ranging from about 15 to 130°C. Amine is employed in an amount ranging from about 1 to 5 equivalents, preferably from about 1.1 to 3 equivalents. The reaction time ranges from several minutes to several days, preferably from about 15 minutes to about two days.

The compound (XV) or a salt thereof thus produced is processed with a base to cause ring-closure reaction to thereby produce a thieno [2,3-d] pyrimidine derivative (XVI). The ring-closure reaction is conducted in a solvent which does not affect adversely on the reaction. The solvent is exemplified by alcohols such as methanol, ethanol or propanol, and ethers such as dioxane or tetrahydrofuran.

As the base, use is made of, for example, an alkali metal alkoxide such as sodium methylate, sodium ethylate or sodium isopropoxide, and an alkali metal hydride such as sodium hydride.

The amount of the base to be employed ranges from 1 to 5 equivalents, preferably from about 1.5 to 3 equivalents, relative to 1 equivalent of the compound (XV).

The reaction temperature ranges from about 10°C to the boiling point of the solvent then employed, preferably from about 25°C to the boiling point of the

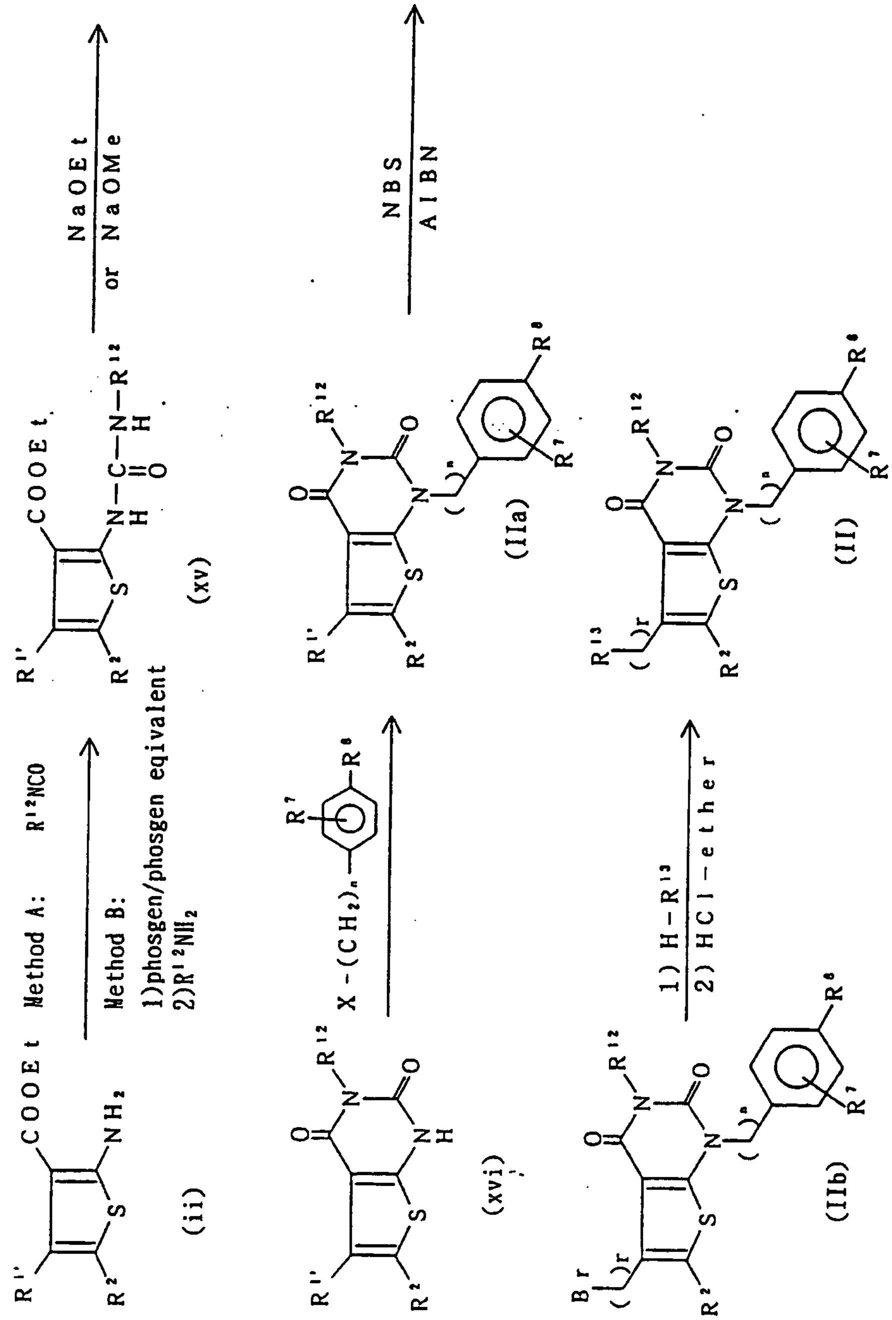
solvent then employed.

The reaction time ranges from several minutes to several days, preferably from about 10 minutes to two days.

The compound (XVI) and a halogenated aralkyl derivative are stirred, in the presence of a base (e.g. an organic base such as pyridine or triethylamine), in a solvent which does not affect adversely on the reaction (e.g. amides such as dimethylformamide or dimethylacetamide), at about 10 to 100°C, to produce a 2,4-dioxothieno[2,3-d]pyrimidine derivative (IIa). Subsequently, the said compound (IIa) is stirred together with N-bromosuccinimide (NBS) in a solvent which does not affect adversely on the reaction (e.g. halogenated hydrocarbons such as carbon tetrachloride or chloroform), in the presence of α, α'-azobisisobutyronitrile, to thereby produce the compound (IIb). Further, the said compound is stirred together with various amines, in the presence of a base, in a solvent which does not affect adversely on the reaction (e.g. amides such as dimethylformamide or dimethylacetamide, nitriles such as acetonitrile, alcohols such as ethanol), at temperatures ranging from about 10 to 100°C, to thereby produce the compound (II). When necessary,the said compound is made into a corresponding salt with a suitable acid (e.g. hydrochloric acid or oxalic acid).

The foregoing Production Method 10 is shown by Scheme 10:

Scheme 10



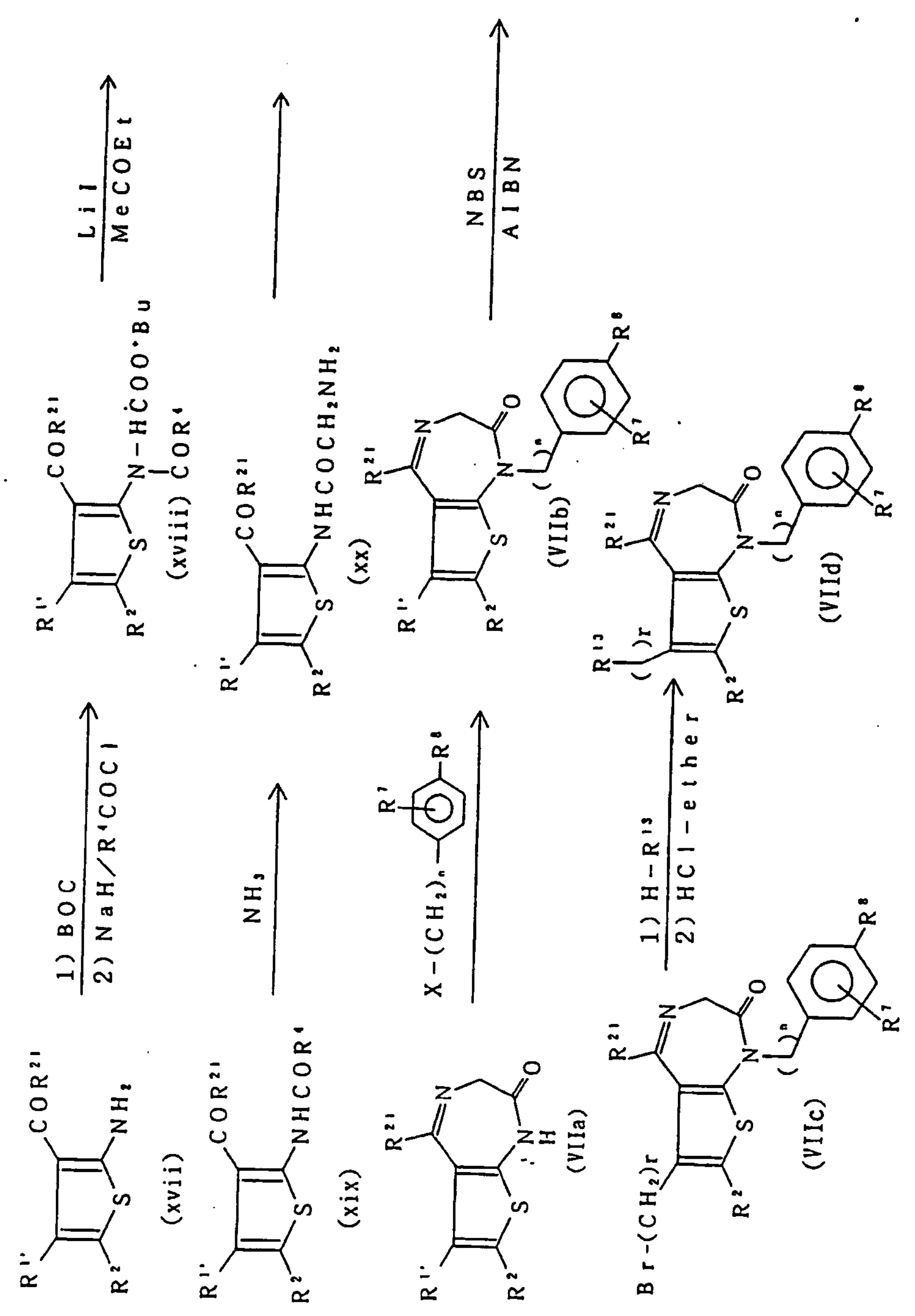
wherein each symbol is of the same meaning as defined above.

[Production Method 11]

The amino group of a 2-aminothiophene derivative (xvii) was protected (e.g. Boc), which was stirred, in accordance with the method of T. Hirohashi et al. [Ger. Pat., 2155403 (1972), among others] or the method of M. Nakanishi et al. [Jap. Pat., 73, 01664 (1973), among others], together with a halogenated acyl derivative, in the presence of a base, in a solvent which does not affect adversely on the reaction (e.g. amides such as dimethylformamide or dimethylacetamide) at temperatures ranging from about 0 to 100°C to give a derivative (xviii), which was stirred together with a suitable salt (e.g. lithium iodide) in a suitable solvent (e.g. acetone or methyl ethyl ketone) to give a derivative (xix), which was subjected to substitution reaction with a suitable amine (e.g. ammonia) to give a derivative (xx), which was stirred in a solvent which does not affect adversely on the reaction (e.g. toluene, dimethylformamide, dimethylacetamide, methanol or ethanol), when necessary in the presence of a suitable catalyst (e.g. sodium ethoxide or toluenesulfonic acid) at temperatures ranging from about 30 to 120°C, to cause dehydro-cyclization to thereby produce a derivative (VIIa). The said compound was stirred, together with a halogenated aralkyl derivative, in the presence of a base (e.g. organic bases including potassium carbonate, pyridine and triethylamine), in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethylacetamide), at temperatures ranging from about 10 to 100°C to give a 2-oxothieno [2,3-e] azepine derivative (VIIb). Subsequently, the said compound (VIIb) was stirred together with N-bromosuccinimide (NBS) in a solvent

(e.g. halogenated hydrocarbons including carbon tetrachloride and chloroform), in the presence of α,α'-azobisisobutyronitrile, at temperatures ranging from about 30 to 100°C, to give a compound (VIIc). The said compound was stirred with various amines in the presence of a base, in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethylacetamide, nitriles including acetonitrile, and alcohols including ethanol) at temperatures ranging from about 10 to 100°C to give a compound (VId). When necessary, the said compound was made into a corresponding salt with a suitable acid (e.g. hydrochloric acid or oxalic acid). The foregoing Production Method 2 is shown in Scheme 11:

Scheme 11



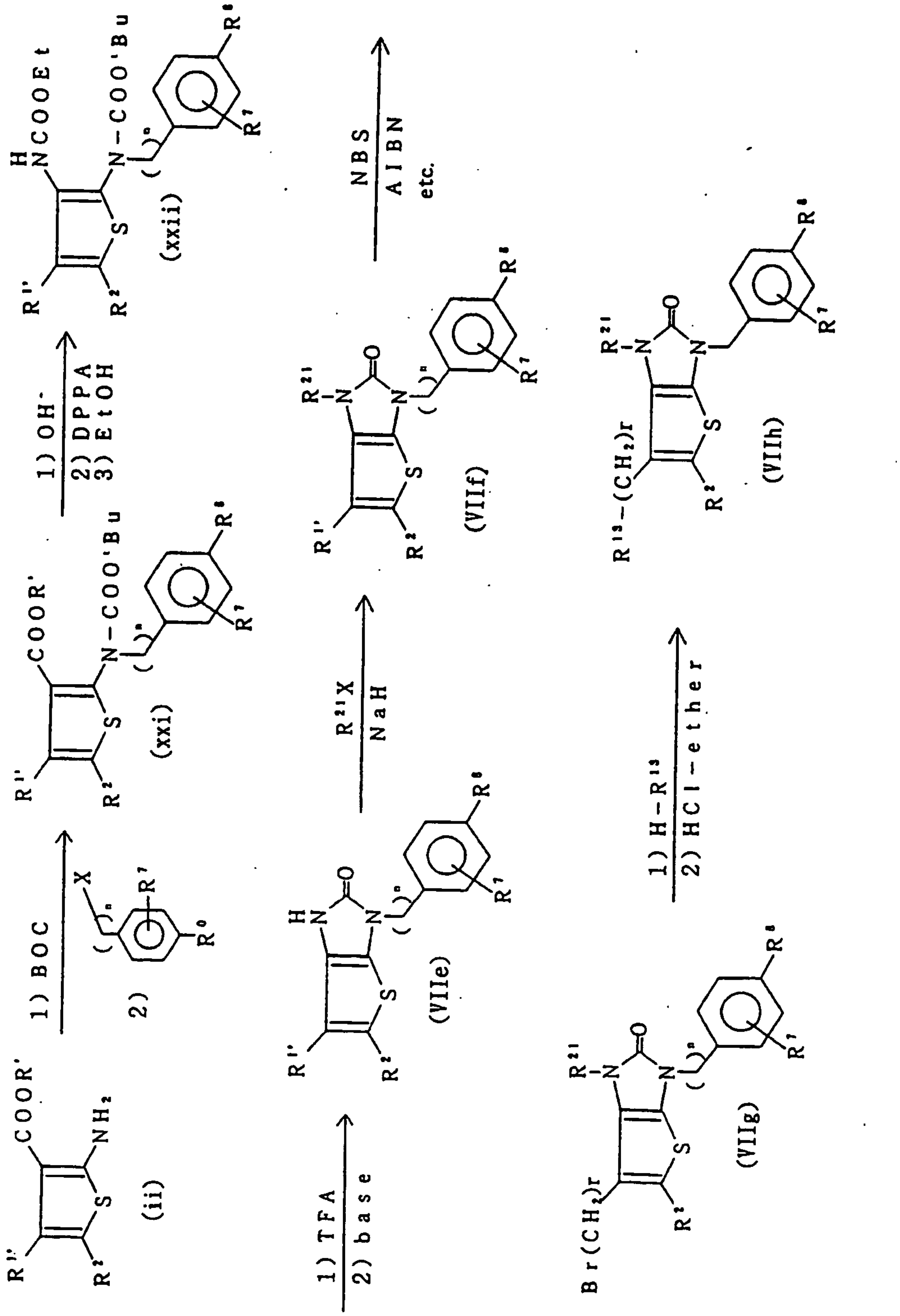
wherein each symbol is of the same meaning as defined above.

[Production Method 12]

The amino group of a 2-aminothiophene derivative producible by the method described in Production Method 1 was protected (e.g. Boc), which was stirred together with a halogenated aralkyl derivative, in the presence of a base (e.g. organic bases including potassium carbonate, pyridine and triethylamine), in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethylacetamide), at temperatures ranging from about 10 to 100°C, to give a derivative (xxi), which was subjected to alkali hydrolysis with a suitable alkali (e.g. sodium hydroxide) in a suitable solvent (e.g. methanol, tetrahydrofuran), and, the derivative thus produced was stirred together with DPPA in a solvent which does not affect adversely on the reaction (e.g. toluene, tetrahydrofuran, dimethylformamide, dimethylacetamide, ethanol) at temperatures ranging from about 0 to 100°C, and the resultant was made into a carbamic acid ester derivative (xxii) with a suitable alcohol (e.g.ethanol). The said derivative was stirred, in the presence of a base (e.g. sodium ethoxide), in a solvent which does not affect adversely on the reaction (e.g. dimethylformamide, dimethylacetamide), at temperatures ranging from about 0 to 100°C to give a thieno[2,3-d] imidazol-2-one derivative (VIIe). The said compound was stirred together with a halogenated alkyl derivative, in the presence of a base, in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide, dimethylacetamide), at temperatures ranging from about 0 to 100°C to give a compound (VIIf). Subsequently, the said compound (VIIf) was stirred, together with N-bromosuccinimide (NBS), in a

solvent which does not affect adversely on the reaction (e.g. halogenated hydrocarbons including carbon tetrachloride and chloroform), in the presence of α,α'-azobisisobutyronitrile, at temperatures ranging from about 30 to 100°C to give a compound (VIIg). The said compound was further stirred, together with various amine, in the presence of a base, in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethylacetamide, nitriles including acetonitrile, alcohols including ethanol), at temperatures ranging from about 10 to 100°C to produce a compound (VIIh). The said compound, when necessary, was made into a corresponding salt with a suitable acid (e.g. hydrochloric acid, oxalic acid). The foregoing Production Method 12 is shown in Scheme 12:

Scheme 12



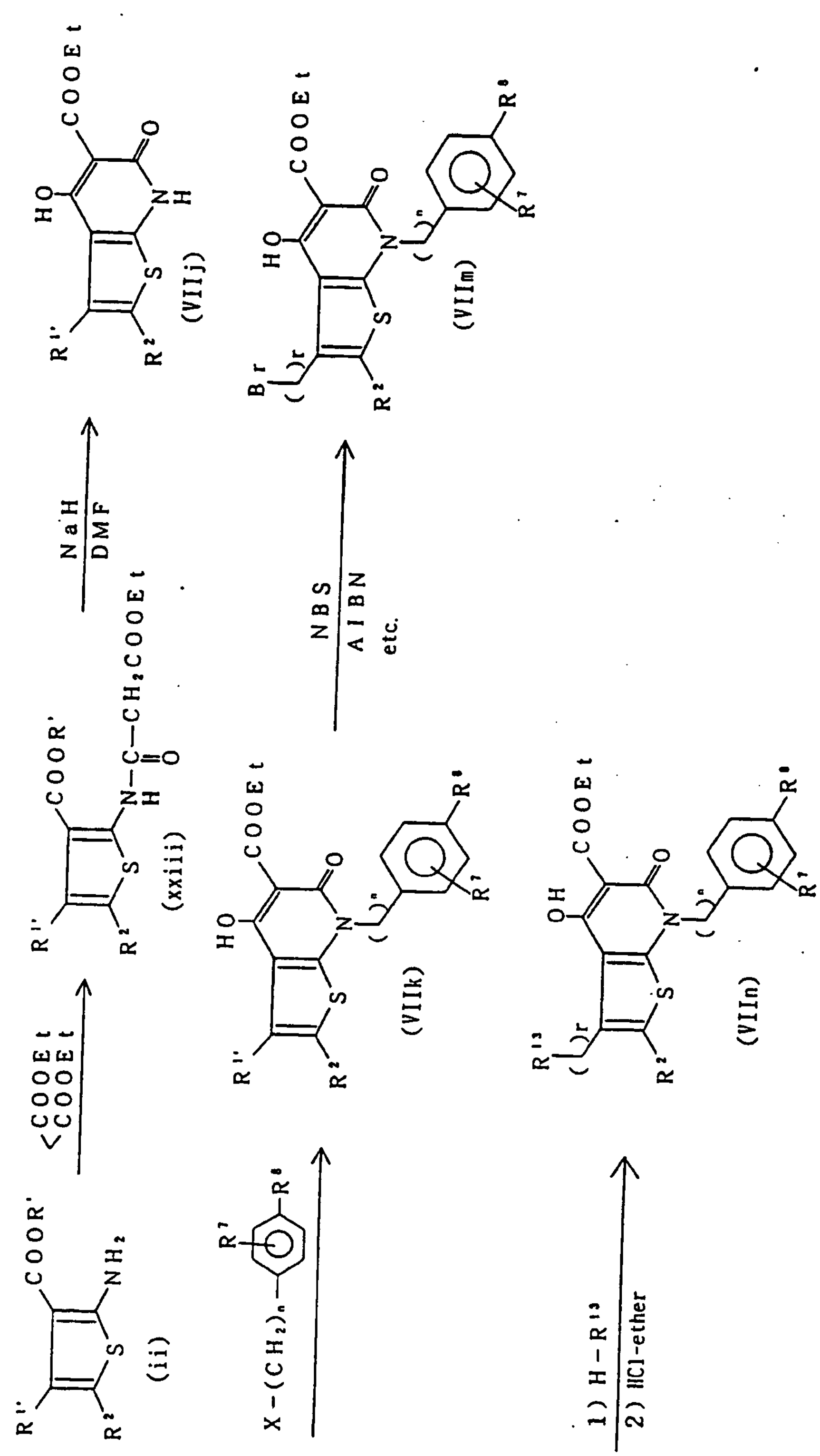
wherein each symbol is of the same meaning as defined above.

[Production Method 13]

Starting from a 2-aminothiophene derivative (ii) producible by the method described in Production Method 1 or a salt thereof, 4,5-dihydro-7-hydroxy-5-oxothieno [3,2-b] pyridine-6-carboxylic acid ethyl derivative (VIIj) was produced by the method of J. M. Barker et al. [J. Chem. Res. (M), 1980, 113; J. Chem. Res. (s), 6(1980)]. More specifically, the 2-aminothiophene derivative (ii) or a salt thereof was allowed to react with malonic acid ester to give the compound (xxii), which was stirred, in the presence of a suitable base (e.g. sodium hydride), in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethyl acetamide), at temperatures ranging from about 10 to 100°C to give the derivative (VIIj). The said derivative (VIIj) was stirred, together with a halogenated aralkyl derivative, in the presence of a base (e.g. organic bases including potassium carbonate, pyridine and triethylamine), in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethyl acetamide), at temperatures ranging from about 10 to 100°C to give a derivative (VIIk), and,the said derivative was stirred, together with N-bromosuccinimide (NBS), in a solvent which does not affect adversely on the reaction (e.g. halogenated hydrocarbons including carbon tetrachloride and chloroform), in the presence of α,α'-azobisisobutyronitrile, at temperatures ranging from about 30 to 100°C to give the compound (VIIm). Further, the said compound was stirred, together with various amines, in the presence of a base, in a solvent which does not affect adversely on the reaction (e.g. amides including dimethylformamide and dimethyl acetamide,

nitriles including acetonitrile, alcohols including ethanol), at temperatures ranging from about 10 to 100°C to produce the compound (VIIn). When necessary, the said compound was made into a corresponding salt with a suitable acid (e.g. hydrochloric acid, oxalic acid).The foregoing Production Method 13 was shown in Scheme 13:

Scheme 13

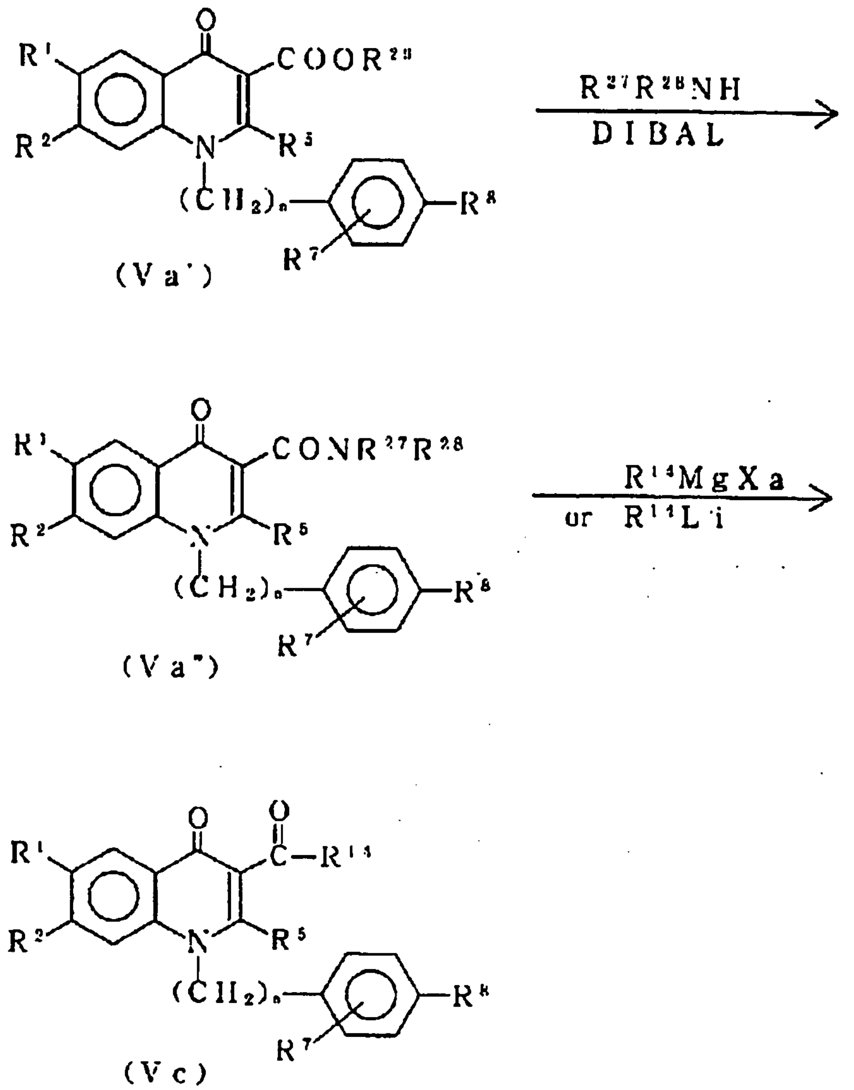

(ii)
(xxiii)
(VIIj)
(VIIk)
(VIIm)
(VIIn)
NaH
DMF
NBS
AIBN
etc.
1) H-R13
2) HCl-ether

wherein each symbol is of the same meaning as defined above.

[Production Method 14]

In a suitable solvent which does not affect adversely on the reaction (e.g. halogenated hydrocarbons including dichloromethane, and ethers including tetrahydrofuran, ethyl ether and dioxane), the 1,4-dihydro-4-oxoquinoline-3-carboxylic acid ester derivative (Va') was stirred, together with an aluminum amide derivative produced from a suitable aluminum reagent [e.g. trimethyl aluminum, triethyl aluminum or diisobutyl aluminum hydride (DIBAL)] and amines, at temperatures ranging from about 10 to 100°C to give a 1,4-dihydro-4-oxoquinoline-3-carboxylic acid amide derivative (Va"). The said derivative was stirred, together with a Grignard reagent, in a suitable solvent (e.g. tetrahydrofuran and ethyl ether) at temperatures ranging from 0 to 80°C to give a corresponding ketone derivative (Vc). The above production method 14 is shown in Scheme 14:

Scheme 14



wherein R^{26} is alkyl or aryl, R^{27} and R^{28} are each hydrogen or hydrocarbon residue, and other symbols are of the same meaning as defined in the foregoing.

The alkyl and aryl shown by the above-mentioned R^{26} is of the same meaning as defined in the foregoing.

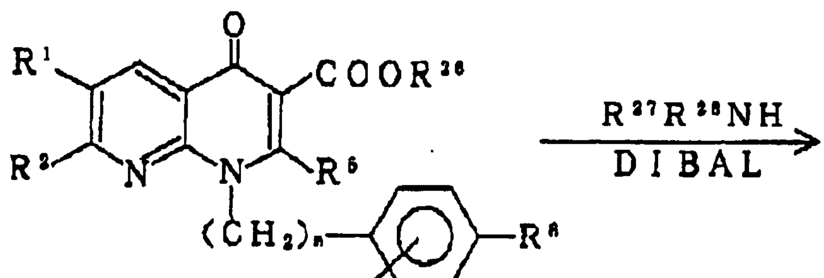
The hydrocarbon residues shown by the above-mentioned R^{27} and R^{28} are of the same meaning as the hydrocarbon residue in the optionally substituted carbonyl group with a hydrocarbon residue shown by the

above-mentioned R'.

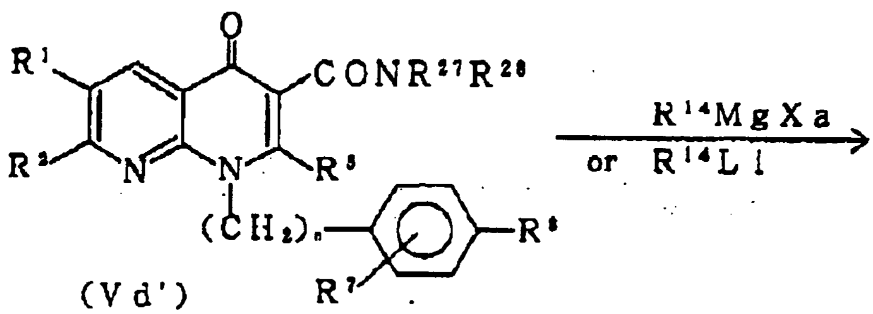
[Production Method 15]

In a suitable solvent which does not affect adversely on the reaction (e.g. halogenated hydrocarbons including dichloromethane, and ethers including tetrahydrofuran, ethyl ether and dioxane), 1,4-dihydro-4-oxopyrido [2,3-b] pyridine-3-carboxylic acid ester derivative (Vd) is stirred, together with an aluminum amide derivative produced from a suitable aluminum reagent [e.g. trimethyl aluminum, triethyl aluminum and diisobutyl aluminum hydride (DIBAL)] and amines, at temperatures ranging from about 10 to 100°C to give a 1,4-dihydro-4-oxopyrido[2,3-b]pyridine-3-carboxylic acid amide derivative (Vd'). The said derivative is stirred, together with a Grignard reagent, in a suitable solvent which does not affect adversely on the reaction (e.g.tetrahydrofuran and ethyl ether), at temperatures ranging from about 0 to 80°C to give a corresponding ketone derivative (Ve). The production method is shown in Scheme 15:

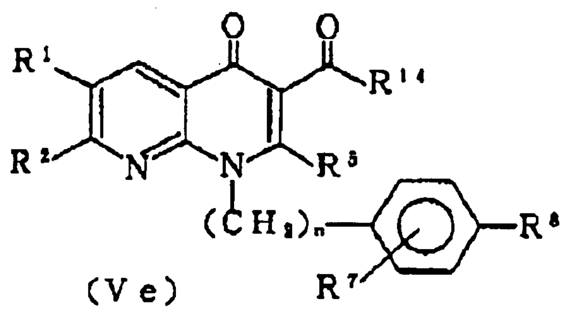
Scheme 15



(Vd)



(Vd')



(Ve)

wherein R^{26} is alkyl or aryl, R^{27} and R^{28} are each hydrogen or hydrocarbon residue, and other symbols are of the same meaning as defined above.

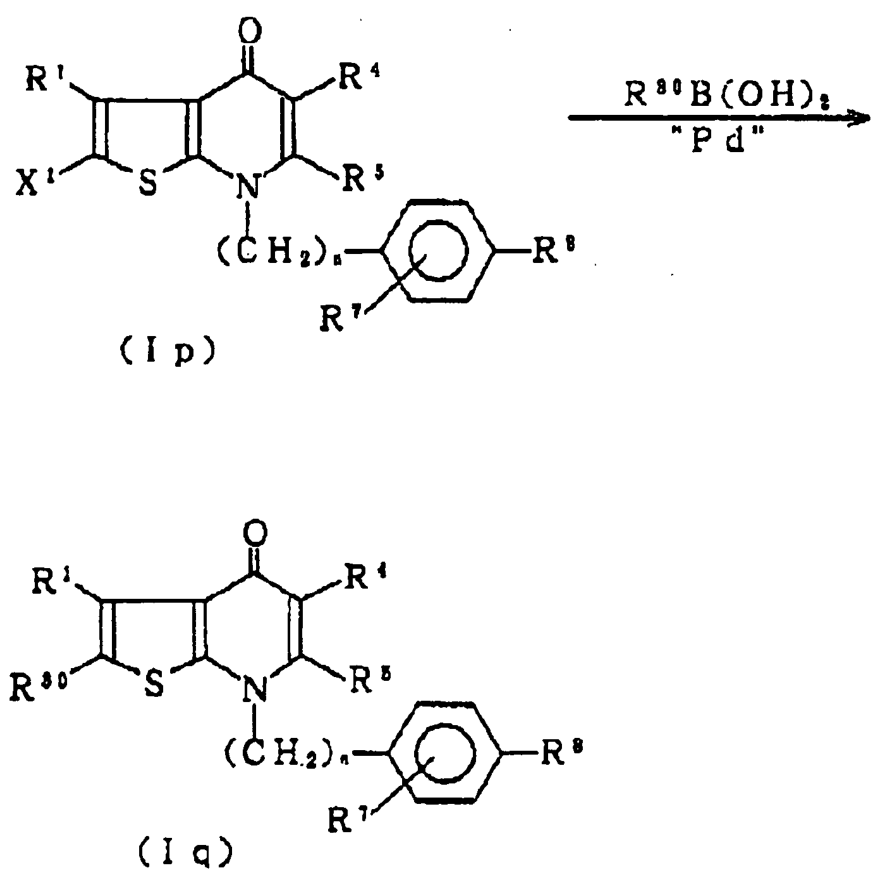
The alkyl and aryl shown by the above R^{26} are of the same meaning as defined above.

The hydrocarbon residue shown by the above R^{27} and R^{28} is of the same meaning as the hydrocarbon residue in the carbonyl group optionally substituted with hydrocarbon residue shown by the above-mentioned R'.

[Production Method 16]

In a suitable solvent which does not affect adversely on the reaction (e.g. ethers including 1,2-dimethoxyethane, tetrahydrofuran and dioxane and alcohols including ethyl alcohol). To the solution is added, in the presence of equimolar to an excess amount (2 to 10 equivalents) of a suitable base (e.g. sodium carbonate), a suitable aryl boric acid derivative (e.g. phenyl boric acid, 3-methoxyphenyl boric acid and 4-ethoxycarbonyl phenyl boric acid). To the mixture is added, in the streams of an inert gas (e.g. argon gas), a suitable catalyst [e.g. palladium metal including tetrakis (triphenylphosphine) palladium]. The mixture is stirred for a period ranging from several minutes to several hours at temperatures ranging from about 10 to 100°C. Insolubles are removed to leave the desired derivative (Iq). The foregoing production method 16 is shown in Scheme 16:

Scheme 16



wherein R^{30} is an optionally substituted aryl group, and other symbols are of the same meaning as defined above.

As salts of the compounds of this invention obtained thus above, physiologically acceptable acid addition salts are preferable. Examples of such salts include those with an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid) or those with an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, bezenesulfonic acid, and p-toluenesulfonic acid). Further, when the compound (I) of this invention has an acid group such as -COOH, the compound(I) may form a salt with an inorganic base (e.g. an alkali metal or alkaline earth metal such as sodium, potassium, calcium and magnesium; ammonia) or an organic base (e.g. trimethylamine, triethylamine, pyridine, picolin, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine).

Especially preferable examples of the compounds or their salts of this invention include 3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2-methoxybenzyl)-2-(4-methoxyphenyl)-4-oxothieno[2,3-b]pyridine-5--carboxylic acid ethyl ester, (3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2-fluorobenzyl)-2-(4-methoxyphenyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester, 2-(4-acetylaminophenyl)-3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2-fluorobenzyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester, 5-benzylmethylaminomethyl-1-(2-chloro-6-fluorobenzyl)-2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-3-phenylthieno[2,3-d]pyrimidine, 5-benzoul-3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-4-oxo-2-(4-propionylaminophenyl)thieno[2,3-b]pyridine,

5-benzoyl-3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine, 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-5-isobutyryl-4-oxo-2-(4-propionylaminophenyl)thieno[2,3-b]pyridine, 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-5-isobutyryl-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine, 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine-5-(N-isopropyl)carboxamide, 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine-5-(N-isopropyl-N-methyl)carboxamide, 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-N'-methylureidophenyl)-4-oxothieno[2,3-b]pyridine-5-(N-benzyl-N-methyl)carboxamide or their salts.

The compounds or salts thereof of the present invention produced thus above can be isolated and purified by a conventional separating means such as recrystallization, distillation and chromatography. In the case where the compound (I) is produced in the free form, it can be converted to a salt thereof by a _per se_ conventional means or a method analogous thereto. On the contrary, when it is obtained in the form of a salt, it can be converted to its free form or to any other salt.

In the case where the compound or a salt thereof of the present invention is an optically active compound, it can be separated into d-compound and l-compound by means of a conventional optical resolution.

Since the compounds of this invention have a GnRH antagonistic activity and low in toxicity, they can be safely used for the therapy of male hormone or female hormone dependent diseases as well as the therapy of

diseases caused by excess secretion of these hormones, in warm-blooded animals (e.g. human, monkey, cow, horse, dog, cat, rabbit, rat and mouse), suppressing the secretion of gonadotropic hormone by the action of GnRH receptor antagonistic action. More specifically, the compounds of this invention are effective as a prophylactic or therapeutic agent for the prevention or treatment of several hormone dependent diseases, for example, a sex hormone dependent cancer (e.g. prostate cancer, cancer of the uterine cervix, breast cancer, pituitary adenoma), benign prostatic hypertrophy, myoma of the uterus, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, polycystic ovary syndrome and acne vulgaris. And, the compounds of this invention are also effective as a fertility controlling agent in both sexes (e.g. pregnancy controlling agents and menstrual cycle controlling agents). The compounds of this invention can be further used as a contraceptive of male or female and, as an ovulation-inducing agent of female. The compound of this invention can be used as an infertility treating agent by using a rebound effect owing to a stoppage of administration thereof. Further, the compounds of this invention are useful as modulating estrous cycles in animals in the field of animal husbandry, and as an agent for improving the quality of edible meat or promoting the growth of animals. Besides, the compounds of this invention are useful as an agent of spawning promotion in fish. While the compounds of this invention can be used singly, they can also effectively be used by administering in combination with a steroidal or non-steroidal antiandrogenic agent. The compound of this invention can be used for the suppressing a passing ascent of testosterone concentration in plasma, the ascent which occurs in administration of GnRH super antagonist such as

leuprorelin acetate. The compound of this invention can effectively be used by administering in combination with a chemoterapeutic agent for cancer. In treatment of prostate cancer, examples of the chemoterapeutic agent include Ifosfamide, UFT, Adriamycin, Peplomycin, Cisplatin and the like. In treatment of breast cancer, examples of the chemoterpeutic agent include Cyclophohamide, 5-FU-, UFT, Methotrexate, Adriamycin, Mitomycin C, Mitoxantrone and the like.

When the compound of this invention is employed, in the field of animal husbandry or fisheries, as prophylactic and therapeutic agents of the above-mentioned diseases, is can be administered orally or non-orally in accordance with per se known means. It is mixed with a pharmaceutically acceptable carrier and usually administered orally as a solid preparation such as tablet, capsule, granule or powder, or non-orally as intravenous, subcutaneous or intramuscular injection, or as suppository or sublingually administrable tablet. Further, it is sublingually, subcutaneously or intramuscularly administered as a prolonged release formulation such as sublingually administrable tablets, or microcapsules. The daily dose varies with the degree of affliction; age, sex, body weight and difference of sensitivity of the subject to be administered; the time and intervals of administration, properties, dosage forms and kinds of the medicinal preparation; and kinds of the effective components, and it ranges usually, though not specifically limited, from about 0.01 to 10 mg, preferably from about 0.02 to 2 mg, more preferably from about 0.01 to 1 mg, relative to 1 kg body weight of warm-blooded animals, which is administered usually once daily or by 2 to 4 divided dosages. The daily dose when used in the field of animal husbandry or fishery varies with the conditions analogous to those mentioned above, it ranges, relative

to 1 kg body weight of the subject animal or fish, from about 0.001 to 5 mg, preferably from about 0.002 to 2 mg, once or 2 to 3 divided dosages.

As the above-mentioned pharmaceutically acceptable carriers, conventional various organic or inorganic carriers are used, and they are incorporated as excipients, lubricants, binders and disintegrants in solid compositions; and as solvents, solubilisers, suspending agents, isotonizing agents, buffering agents and pain-easing agents in liquid compositions. And, depending on necessity, further additives such as preservatives, anti-oxidants, coloring agents and sweeteners can also be used.

Preferable examples of the above-mentioned excipients include lactose, sugar, D-mannito, starch, crystalline cellulose and more volatile silicon dioxide. Preferable examples of above-mentioned lubricants include magnesium stearate, calcium stearate, talc and colloid silica. Preferable examples of the above-mentioned binders include crystalline cellulose, sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxymethyl cellulose and polyvinyl pyrrolidone. Preferable examples of the above-mentioned disintegrants include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, cross carmelose sodium, cross carmelose sodium and carboxymethyl starch sodium. Preferable examples of the above-mentioned solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil. Preferable examples of the above-mentioned solubilizers include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate. Preferable examples of the above-mentioned suspending agents include surfactants such as stearyl triethanolamine, sodium

lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride and monostearic glyceryl ester; and hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Preferable examples of the above-mentioned isotonizing agents include sodium chloride, glycerin and D-mannitol. Preferable examples of the above-mentioned buffering agents include buffer solutions such as phosphate, acetate, carbonate and citrate. Preferable examples of the above-mentioned pain-easing agents include benzyl alcohol. Preferable examples of the above-mentioned preservatives include para-hydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid. Preferable examples of the above-mentioned anti-oxidants include sulfite and ascorbic acid.

To the compound of this invention, are added, for example, a suspending agent, a solubilizer, a stabilizer, an isotonizing agent and a preservative, then the mixture is formulated, in accordance with a *per se* known method, into an intravenous, subcutaneous or intramuscular injection. These injections can be processed into lyophilized preparations, when necessary, by a *per se* known method.

Examples of the above-mentioned pharmaceutical composition are oral agents (e.g. diluted powders, granules, capsules and tablets), injections, dropping injections, external agents (e.g. transnasal preparations, percutaneous preparations, etc.), ointments (e.g. rectal ointment, vaginal ointment, etc.) and the like.

Such pharmaceutical compositions can be manufactured by a *per se* known method commonly used in

preparing pharmaceutical compositions.

The compound of the present invention or a salt thereof can be made into injections either in a form of an aqueous injection together with dispersing agents [e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 80 (Nikko Chemicals, Japan), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.], preservatives (e.g. methyl paraben, propyl paraben, benzyl alcohol, etc.), isotonizing agents (e.g. sodium chloride, mannitol, sorbitol, glucose, etc.) and the like or in a form of an oily injection by dissolving, suspending or emulsifying in plant oil (e.g. olive oil, sesame oil, cotton seed oil, corn oil, etc.), propylene glycol and the like.

In preparing a pharmaceutical composition for oral use, the compound of the present invention or a salt thereof is molded by compressing, for example, with fillers (e.g. lactose, sucrose, starch, etc.), disintegrating agents (e.g. starch, calcium carbonate, etc.), binders (e.g. starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.) or lubricants (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.) and the like. If necessary, the composition is coated by a per se known method with an object of masking the taste, enteric coating or long-acting. Examples of the coating agent therefore are hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, pluronic F 68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (a copolymer of methacrylic acid with acrylic acid; manufactured by Rohm, Germany), red oxide of iron and the like. Subcoating layer may be provided between the

enteric coating and the core according to per se known method.

In preparing an external composition, the compound of the present invention or a salt thereof as it is or a salt thereof is subjected to a per se known method to give a solid, semisolid or liquid agent for external use. For example, the solid preparation is manufactured as follows. Thus, the compound of the present invention as it is or after adding/mixing fillers (e.g. glycol, mannitol, starch, microcrystalline cullulose, etc.), thickeners (e.g. natural gums, cellulose derivatives, acrylic acid polymers, etc.) and the like thereto/therewith is made into a powdery composition. With respect to the liquid composition, an oily or aqueous suspension is manufactured by the manner nearly the same as in the case of the injection. In the case of a semisolid composition, the preferred one is an aqueous or oily gel or an ointment. Each of them may be compounded with a pH adjusting agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), an antiseptic agent (e.g. p-hydroxybenzoates, chlorobutanol, benzalkonium chloride, etc.) and the like.

In the manufacture of an ointment for example, the compound of the present invention or a salt thereof can be made into an oily or an aqueous solid, semisolid or liquid ointment. Examples of the oily base material applicable in the above-mentioned composition are glycerides of higher fatty acids [e.g. cacao butter, Witepsols (manufactured by Dynamite-Nobel), etc.], medium fatty acids [e.g. Miglyols (manufactured by Dynamite-Nobel), etc.] and plant oil (e.g. sesame oil, soybean oil, cotton seed oil, etc.) and the like. Examples of the aqueous base material are polyethylene glycols and propylene glycol and those of the base

material for aqueous gel are natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers, etc.

Best Mode for Carrying Out of the Invention

By way of the following Reference Examples, Working Examples and Test Examples, the present invention will be described more specifically, but they are not intended to limit the scope of this invention thereto.

^{1}H-NMR spectra were taken with the Varian GEMINI 200 (200 MHz) type spectrometer, JEOL LAMBDA300 (300MHz) type spectrometer or the Brucker AM 500 (500 MHz) type spectrometer, employing tetramethylsilane as the internal standard. All delta values were expressed in ppm.

The symbols used in the present specification have the following meanings:

s: singlet, d: doublet, t: triplet, dt: double triplet, m: multiplet, br: broad

Reference Example 1

2-Amino-5-phenylthiophene-3-carboxylic acid ethyl ester

To a mixture of ethyl cyanoacetate (6.1 g, 50 mmol), sulfur (1.61 g, 50 mmol) triethylamine (3.5 ml, 25 mmol) and dimethylformamide (10 ml) was added dropwise, with stirring at 45°C, phenylacetaldehyde (50% diethylphthalate solution; 12.05 g, 50 mmol) for 20 minutes. The mixture was stirred for 9 hours at 45°C, and the reaction mixture was concentrated. The resulting residue was extracted with ethylacetate. The extract was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel, followed by crystallization from ether-hexane to give slightly yellow plates (5.55 g, 45%), m.p.124.5-125.5°C (value in literature reference 123-124°C).

Elemental Analysis for $C_{13}H_{13}NO_2S$:

	C(%)	H(%)	N(%)
Calcd.:	63.13 ;	5.30 ;	5.66
Found :	62.99 ;	5.05 ;	5.63

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.37(3H,t,J=7.1Hz), 4.30(2H,d,J=7.1Hz), 5.97(2H,br), 7.17-7.46(6H,m).

IR(KBr): 3448, 3320, 1667, 1590, 1549 cm^{-1}.

Reference Example 2

2-Amino-4-methyl-5-(4-methoxyphenyl)thiophene-3-carboxylic acid ethyl ester

A mixture of 4-methoxyphenylacetone (16.5 g, 0.10 mol), ethyl cyanoacetate (12.2 g, 0.10 mol), ammonium acetate (1.55 g, 20 mmol), acetic acid (4.6 ml, 80 mmol) and benzene (20 ml) was heated for 24 hours under reflux, while removing water produced in the reaction mixture using a Dean and Stark apparatus. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between dichloromethane and an aqueous sodium hydrogencarbonate solution. The organic layer was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling of the solvent under reduced pressure. To an ethanol (30 ml) solution of the residue were added sulfur (3.21 g, 0.10 mol) and diethylamine (10.4 ml, 0.10 mol). The mixture was stirred at 50-60°C for 2h and then concentrated, and the concentrate was extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride solution and dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel, which was the crystallized from ether-hexane to give a pale yellow plates (11.5 g, 40%), m.p.79-80°C.

Elemental Analysis for $C_{15}H_{17}NO_3S$:

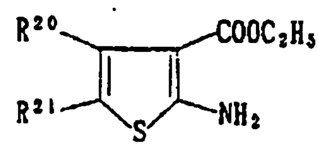
	C(%)	H(%)	N(%)	S(%)
Calcd.:	61.83 ;	5.88 ;	4.81 ;	11.01
Found :	61.81 ;	5.75 ;	4.74 ;	10.82

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.37(3H,t,J=7.1Hz), 2.28(3H,s), 3.83(3H,s), 4.31(2H,q,J=7.1Hz), 6.05(2H,brs), 6.91(2H,d,J=8.8Hz), 7.27(2H,d,J=8.8Hz). IR(KBr): 3426, 3328, 1651, 1586, 1550, 1505, 1485 cm^{-1}. FAB-MS m/z: 291 (M^+)

Reference Example 3

Employing various acetone derivatives in place of 4-methoxyphenylacetone, compounds shown in Table 1 were produced in accordance with substantially the same manner as described in Reference Example 2.

Table 1



R.Ex. 3 Cpd.No.	R^{20}	R^{21}	Yield (%)	m.p. (°C)
1	methyl	phenyl	40	64-65
2	methyl	2-methoxyphenyl	12	70-71

Reference Example 4

{3-Ethoxycarbonyl-5-(4-methoxyphenyl)-4-methylthiophen-2-yl}aminomethylene malonic acid diethyl ester

To the compound produced in Reference Example 2 (10 g, 343.3 mmol) was added diethyl ehoxymethylene malonate (7.45 g, 34.5 mmol). The mixture was stirred for 2 hours at 120°C. After cooling, to the reaction mixture was added ether to precipitate crystals. The crystals were collected by filtration and washed with ether once more, followed by drying over phosphorus pentaoxide under reduced pressure to give pale yellow crystals (14.2 g, 90%), m.p.122-123°C.

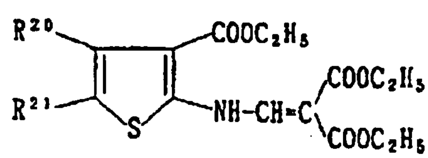
^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.32(3H,t,J=7.1Hz), 1.38(3H,t,J=7.2Hz), 1.41(3H,t,J=7.2Hz), 2.34(3H,s), 3.85(3H,s), 4.25(2H,q,J=7.1Hz), 4.38(2H,q,J=7.2Hz),

4.45(2H,q,J=7.2Hz), 6.95(2H,d,J=8.8Hz), 7.31(2H,d,J=8.8Hz), 8.22(1H,d,J=13.4Hz), 12.74(1H,d,J=13.1Hz).
IR(KBr): 2984, 1720, 1707, 1688, 1653, 1599, 1518, 1499 cm^{-1}.

Reference Example 5

Employing, as starting materials, compounds produced in Reference Example 3 or commercially available various thiophene compounds, in accordance with substantially the same manner as described in Reference Example 4, the compounds shown in Table 2 were produced.

Table 2



R.Ex. 5 Cpd.No.	R^{20}	R^{21}	Yield (%)	m.p. (°C)
1	methyl	phenyl	92	108-109
2	phenyl	methyl	92	137-138
3	methyl	H	92	132-133
4	methyl	2-methoxyphenyl	100	amorphous

Reference Example 6

{3-carboxy-5-(4-methoxyphenyl)-4-methylthiophen-2-yl}aminomethylene malonic acid diethyl ester

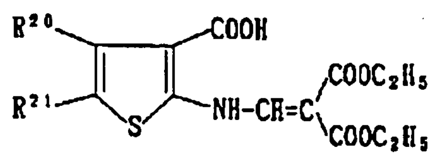
To a solution of the compound produced in Reference Example 4 (7.0 g, 15.2 mmol) in dioxane (20 ml) was added a solution of potassium hydroxide (5.0 g, 75.7 mmol) in ethanol (30 ml) at 60-70°C with stirring. The mixture was stirred for one hour at the same temperature range, which was allowed to stand for one hour at room temperature. To the reaction mixture was added 2N HCl (40 ml, 80 mmol) with ice-cooling. The

reaction mixture was concentrated under reduced pressure. Resulting yellow precipitate was collected by filtration, which was washed with a mixture of cold water and ethanol, followed by drying over phosphorus pentaoxide under reduced pressure to give a yellow powder (6.1 g, 93%), m.p. 184-187°C.
^{1}H-NMR (200MHz, DMSO-d_6) δ: 1.24(3H,t,J=7.1Hz), 1.28(3H,t,J=7.2Hz), 2.30(3H,s), 3.80(3H,s), 4.15(2H,q,J=7.1Hz), 4.24(2H,q,J=7.2Hz), 7.03(2H,d,J=8.7Hz), 7.37(2H,d,J=8.7Hz), 8.08(1H,d,J=13.6Hz), 12.41(1H,d,J=13.6Hz).
IR(KBr): 3422, 2980, 1719, 1653, 1607, 1551, 1512 cm^{-1}.

Reference Example 7

Employing compounds obtained in Reference Example 5 as starting materials, in accordance with substantially the same manner as Reference Example 6, the compounds shown in Table 3 were produced.

Table 3



R.Ex. 7 Cpd.No.	R^{20}	R^{21}	Yield (%)	m.p. (°C)
1	methyl	phenyl	98	187-190
2	phenyl	methyl	65	173-175
3	methyl	H	94	187-189
4	methyl	2-methoxyphenyl	88	167-169

Reference Example 8

4-Hydroxy-2-(4-methoxyphenyl)-3-methylthieno[2,3-b]pyridine-5-carboxylic acid ethyl ester

To polyphosphoric ester (PPE) (90 ml) was added the compound produced in Reference Example 6 (6.0 g, 13.8 mmol) in small portions at 190°C with stirring.

The mixture was stirred for 30 minutes at the same temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with ethylacetate. The extract solution was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel to give a yellow powder (3.65 g, 77%). As the sample for elemental analysis, the powder was recrystallized from ethanol to give yellow crystals, m.p.162-163°C.

Elemental Analysis for $C_{18}H_{17}NO_4S$:

	C(%)	H(%)	N(%)	S(%)
Calcd.:	62.96 ;	4.99 ;	4.08 ;	9.34
Found :	62.89 ;	5.04 ;	4.01 ;	9.34

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.47(3H,t,J=7.1Hz), 2.63(3H,s), 4.87(3H,s), 4.49(2H,q,J=7.1Hz), 6.99(2H,d,J=8.8Hz), 7.44(2H,d,J=8.8Hz), 8.84(1H,s), 12.11(1H,s).

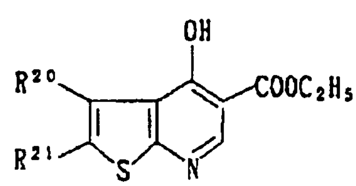
IR(KBr): 3434, 2992, 1692, 1601, 1582, 1535, 1504 cm^{-1}.

FAB-MS m/z: 344 (MH^+)

Reference Example 9

Employing compounds produced in Reference Example 7 as starting materials, in accordance with substantially the same manner as described in Reference Example 8, the compounds shown in Table 4 were produced.

Table 4



R.Ex. 9 Cpd.No.	R^{20}	R^{21}	Yield (%)	m.p. (°C)
1	methyl	phenyl	60	155-157
2	phenyl	methyl	69	146-147
3	methyl	H	21	175-177
4	methyl	2-methoxyphenyl	73	amorphous

Reference Example 10

4-Hydroxy-2-(4-nitrophenyl)-3-methylthieno[2,3-b]pyridine-5-carboxylic acid ethyl ester

To a solution of the compound 1 produced in Reference Example 9 (3.76 g, 12.0 mmol) in conc. sulfuric acid (10 ml) was added dropwise, a solution of sodium nitrate (1.27 g, 15.0 mmol) in conc. sulfuric acid (5 ml) with ice-cooling. The mixture was stirred for 30 minutes at the same temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with chloroform. The extract was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel to give a yellow powder, which was recrystallized from ethanol to afford yellow crystals (1.75 g, 41%), m.p.260-261°C.

Elemental Analysis for $C_{17}H_{14}N_2O_5S$:

	C(%)	H(%)	N(%)
Calcd.:	56.98 ;	3.94 ;	7.82
Found :	56.66 ;	3.91 ;	7.86

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.49(3H,t,J=7.1Hz), 2.70(3H,s), 4.51(2H,q,J=7.1Hz), 7.70(2H,d,J=8.8Hz), 8.34(2H,d,J=8.8Hz), 8.89(1H,s), 12.27(1H,s).

IR(KBr): 3002, 1692, 1605, 1514, 1350, 1290 cm^{-1}.

FAB-MS m/z: 358 (MH^+)

Reference Example 11

4-Hydroxy-5-hydroxymethyl-2-(4-methoxyphenyl)-3-methylthieno[2,3-b]pyridine

To a suspension (6 ml) of lithium aluminum hydride (0.0326 g, 0.87 mmol) in anhydrous tetrahydrofuran was added dropwise a solution of the compound produced in Reference Example 8 (0.20 g, 0.58 mmol) in anhydrous tetrahydrofuran (3 ml) at room temperatures (15-35°C, the same range applies hereinafter). The mixture was then stirred for 30 minutes at room temperature, to which was added an aqueous solution of Rochelle salt. Resulting precipitate was removed by filtration. In this process, when necessary, the reaction mixture was subjected to heating under reflux to complete the reaction. The precipitate was washed with ethyl alcohol and chloroform, which was combined with the filtrate, followed by concentration under reduced pressure. The concentrate was partitioned between ethyl acetate and an aqueous sodium chloride solution. The organic layer was dried ($MgSO_4$), from which the solvent was distilled off under reduced pressure to give white crystals (0.13 g, 74%).

mp > 300°C

^{1}H-NMR (200MHz, DMSO-d_6) δ: 2.55(3H,s), 3.81(3H,s), 4.41(2H,s), 7.03(2H,d,J=8.8Hz), 7.40(2H,d,J=8.8Hz), 7.75(1H,s).

IR(KBr): 3210, 2930, 1613, 1506, 1255 cm^{-1}.

FAB-MS m/z: 302 (MH$^+$)

Reference Example 12

2-Benzoyl-4-hydroxy-3-methylthieno[2,3-b]pyridine-5-carboxylic acid ethyl ester

To a mixture of the compound 3 produced in Reference Example 7 (5.0 g, 15.3 mmol) and anhydrous aluminum chloride (8.6 g, 64.5 mmol) in nitromethane (100 ml) was added dropwise gradually, in an atmosphere of nitrogen with ice cooling, benzoyl chloride (3.6 ml, 31.0 mmol). The mixture was stirred for one hour at room temperature and, then, for 14 hours at 50°C. The reaction mixture was poured into ice-water, followed by

extraction with ethyl acetate. The extract was washed with an aqueous sodium chloride solution, which was dried ($MgSO_4$), then the solvent was distilled off under reduced pressure to give a brownish powder (7.58 g). The powder was added, in small portions, to polyphosphoric acid ester (PPE), while stirring at 120°C. The mixture was stirred for 90 minutes at the same temperature, which was then poured into ice-water, followed by extraction with ethyl acetate. The extract was washed with an aqueous sodium chloride solution and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residue was chromatographed on silica gel to give a yellow powder (0.82 g, 16%). As the sample for elemental analysis, the powdery product was recrystallized from chloroform-methanol to give a yellow crystals. m.p.241-243°C

Elemental Analysis for $C_{18}H_{15}NO_4S \cdot 0.25H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	62.51 ;	4.52 ;	4.05
Found :	62.77 ;	4.22 ;	4.30

^{1}H-NMR (200MHz, $CDCl_3$-CD_3OD) δ: 1.49(3H,t,J=7.1Hz), 2.71(3H,s), 4.53(2H,q,J=7.1Hz), 7.49-7.70(3H,m), 8.96(1H,s).

IR(KBr): 3004, 1692, 1638, 1603, 1582, 1537, 1431 cm^{-1}.

Reference Example 13

2-Phenylacetyl-4-hydroxy-3-methylthieno[2,3-b]pyridine-5-carboxylic acid ethyl ester

Employing the compound 3 (10.0 g, 30.55 mmol) produced in Reference Example 7, in substantially the same manner as in Reference Example 12, using phenylacetyl chloride in place of benzoyl chloride, the above-titled compound (1.47 g, 14%) were produced. m.p.208-214°C

Elemental Analysis for $C_{19}H_{17}NO_4S \cdot 0.1EtOAc$:

	C(%)	H(%)	N(%)
Calcd.:	63.98 ;	4.93 ;	3.85

Found : 64.25 ; 4.66 ; 3.52

^{1}H-NMR (200MHz, $CDCl_3$-CD_3OD) δ: 1.47(3H,t,J=7.1Hz), 2.99(3H,s), 4.20(2H,s), 4.49(2H,q,J=7.1Hz), 7.26-7.41(5H,m), 8.96(1H,s), 12.50(1H,s).

IR(KBr): 3424, 2986, 1694, 1601, 1580, 1535, 1495, 1439 cm^{-1}.

Reference Example 14

2-Bromo-4-hydroxy-3-methylthieno[2,3-b]pyridine-5-carboxylic acid ethyl ester

To a solution of the compound 3 produced in Reference Example 7 (17.8 g, 54.4 mmol) and pyridine (22 ml, 0.272 mmol) in chloroform (120 ml) was added dropwise gradually a solution of bromine (3.4 ml, 66.0 mmol) in chloroform (30 ml). The mixture was stirred for 40 minutes at room temperature, and then, the reaction mixture was concentrated under reduced pressure. To the concentrate was added dilute hydrochloric acid. The resulting crystalline precipitate was collected by filtration, which was washed with water and a small volume of cold ether, followed by drying over phosphorus pentaoxide under reduced pressure to give a brown powder (20 g). This powder was added, in small portions, to polyphosphoric acid ester (PPE) (100 ml) at 120°C under stirring. The mixture was stirred for 90 minutes at the same temperature. The reaction mixture was then poured into ice-water, which was subjected to extraction with ethyl acetate. The extract was washed with an aqueous saline solution and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residue was chromatographed on silica gel to give a pale yellow powder (9.93 g, 58%). As the sample for elemental analysis,the powder was recrystallized from chloroform-methanol to give colorless needles, m.p.214-216°C.

Elemental Analysis for $C_{11}H_{10}NO_3SBr$:

C(%)	H(%)	N(%)